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UNIVERZITA KARLOVA
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MUDr. Lucie Undus (Nováková)

Váhové změny u pacientů s Parkinsonovou nemocí, kteří byli léčeni hlubokou mozkovou stimulací

Weight changes in patients with Parkinson's disease treated with Deep Brain Stimulation

Dizertační práce

Školitel: prof. MUDr. Evžen Růžička, DrSc., FCMA, FEAN

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Souhrn

Váhové změny jsou popisovány v literatuře jak v průběhu Parkinsonovy nemoci (PN), tak u pokročilé Parkinsonovy nemoci léčené oboustrannou hlubokou mozkovou stimulací subthalamického jádra (STN DBS). Váhové změny se u pacientů po STN DBS vyskytují často, jsou popisovány v 50-100% případů. V posledních 15 letech byla vyvinuta velká snaha o porozumění mechanismů těchto změn, ale navzdory tomu se i nadále v literatuře objevují protichůdná sdělení. Mezi důvody váhového přírůstku se mimo jiné spekulovalo o zlepšeném hybném stavu, snížení či vymizení mimovolních pohybů, změn v příjmu potravy, redukci dopaminergní léčby, hormonálních faktorech a regionálním efektu stimulace. Hypotézou práce bylo, že i naši pacienti budou přibývat na hmotnosti (studie 1-2). Jelikož mechanismus váhového přírůstku u STN DBS nebyl dosud uspokojivě objasněn, tak jsme v naší druhé práci pracovali s hypotézou, že k váhovým změnám dochází v důsledku dysregulace hormonů a parametrů příjmu potravy (studie 2). Ve třetí práci jsme hypotezovali, že váhový přírůstek souvisí s pozicí aktivního kontaktu elektrody v STN jádru (studie 3).

Cíle práce: Jsou potvrzení váhového přírůstku a souvisejících antropometrických změn u pokročilých PN pacientů po STN DBS, prozkoumání regulace energetické homeostázy měřením laboratorních parametrů příjmu potravy a ověření, zda pozorovaný váhový přírůstek souvisí s polohou aktivního kontaktu elektrody v STN jádru.

Metodika a výsledky: Studie 1 - Retrospektivní studie ve formě strukturovaného dotazníku byla použita ke zhodnocení váhových změn pacientů v souvislosti s aplikací STN DBS. Studie prokazuje signifikantní váhový přírůstek u všech pacientů v porovnání období před a po STN DBS, přičemž pouze u některých pacientů docházelo ke zvýšení hmotnosti i s odstupem jednoho roku. Váhové

změny jsou doprovázeny změnami body mass indexu (BMI) a nebyla nalezena korelace mezi změnami hmotnosti a změnami v Unified Parkinson's Disease Rating Scale (UPDRS), Movement Disorder Society (MDS) skóre dyskinéz ani v levodopa equivalent daily dosage (LEDD). Studie 2 – Antropometrické parametry a hormony zapojené do regulace příjmu potravy (leptin, adiponektin, resistin, ghrelin, cortisol, insulin a thyreotropin) byly měřeny v pravidelných intervalech během období dvanácti měsíců po zavedení elektrod. Nalezli jsme zvýšení hmotnosti, BMI, obvodu pasu i procenta adiposity během celé studie. Signifikantní váhový přírůstek byl pozorován již v prvním měsíci po neurochirurgickém zákroku, naproti tomu se kromě změn hladiny kortizolu, neprokázaly signifikantní změny v testovaných hormonech regulace příjmu potravy. Na základě těchto výsledků se domníváme, že s výjimkou kortizolu nepřispívají změny periferních hormonů k váhovému přírůstku u STN DBS u PN. Studie 3 - T1 vážené MRI obrazy byly vyhotoveny 1 rok po implantaci DBS a byla vypočítána poloha elektrody v STN. Nalezli jsme, že váhový přírůstek souvisí inverzně se vzdáleností kontaktů od stěny III. mozkové komory a že pacienti, kteří měli alespoň jeden kontakt uložen mediálně přibrali na hmotnosti signifikantně více než pacienti s oběma kontakty lokalizovanými laterálně.

Závěry: Potvrdili jsme, že u pacientů s pokročilou PN, kteří jsou léčeni STN DBS, dochází k nárůstu hmotnosti a s ní souvisejícími změnami antropometrických parametrů. Náš výzkum prokázal, že příčinou těchto změn není dysregulace tradičních periferních hormonů příjmu potravy. Dále jsme doložili, že mediální pozice aktivního kontaktu v STN jádře je spojena se signifikantním nárůstem hmotnosti.

Klíčová slova: Parkinsonova nemoc, hluboká mozková stimulace, subthalamické jádro, váhový přírůstek, hormony příjmu potravy

Abstract

Body weight changes have been described in the course of Parkinson's disease (PD) as well as following bilateral deep brain stimulation of the subthalamic nucleus (STN DBS) performed in advanced PD. According to the literature weight changes occur in 50-100% of patients who undergo STN DBS. In the last 15 years extensive efforts have been put in understanding the underlying mechanisms behind the weight changes following STN DBS in advanced PD patients however many sources still report conflicting evidence. Improved motor status, reduction in dyskinesias, decrease in energy expenditure, dopaminergic medication reduction, modification of food intake, hormonal factors, regional effects of stimulation were all speculated to cause this weight gain. We hypothesized that patients who underwent STN DBS procedure in our center would gain weight as reported in the literature (study 1, study 2). The etiology of post STN DBS weight gain has not been fully elucidated up to date, in our second study we further hypothesized that the weight changes are due to dysregulation of food related hormones and parameters (study 2). In the third study we hypothesized that weight gain is associated with position of active electrode contact (study 3).

Aims of the study: The primary aims of our studies were to assess body weight changes and related anthropometric parameters following STN DBS in PD (study 1 and 2), to explore regulation of energy homeostasis and food intake by assessment of laboratory parameters involved in body weight and energy metabolism homeostasis, and to assess whether weight gain observed is dependent on the active electrode contact position in STN, particularly with respect to mediolateral direction (study 3).

Methods and results: Study 1. Retrospective survey in the form of structured questionnaire, was used to evaluate body weight changes in our patients with

advanced PD treated with STN DBS and the survey was repeated year later from the first one. Significant weight gain was found in all patients comparing to pre-DBS period. In the repeated survey only few patients increased further body weight. Study 2. Anthropometric parameters and food- related hormones such as leptin, adiponectin, resistin, ghrelin, cortisol, insulin, and thyroid stimulating hormone were repeatedly measured during a 12 months period following electrode implantation. On average we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period. The significant weight change was already apparent in the first month following the surgery. No significant changes were found in food related hormones and biochemical parameters compared to baseline except a significant decrease in cortisol levels. Thus, we concluded, that changes in traditional peripheral food related hormones do not appear to be cause of weight gain in STN DBS treated PD patients. Study 3. T1 weighted magnetic resonance images were acquired one year after DBS implantation and electrode position within the STN was established. We found that weight gain was inversely related to distance of contacts from the wall of third ventricle and the patients who had at least one contact located medially gained significantly more weight than those with both active contacts located laterally.

Conclusions: In our studies we have confirmed post STN DBS weight gain associated with changes in corresponding anthropometric parameters. Our observations conclude that the weight changes are not caused by dysregulation in traditional peripheral food related hormones and parameters, however we further discovered that patients with at least one contact positioned medially within the STN encountered significantly higher weight gain that those patients with both active contacts localized laterally.

Key words: Parkinson's disease, deep brain stimulation, subthalamic nucleus, weight gain, food intake hormones

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1. Introduction

1.1. Parkinson's disease

Parkinson's disease (PD) is a common neurodegeneration with estimate prevalence of 1% over the age of 60 years. There are currently about 10 million people worldwide living with Parkinson's disease. To date, researches still have a limited understanding of the key molecular events that provoke neurodegeneration in this disease. A prevalent etiologic hypothesis is that PD may result from complex interactions between environmental toxic factors, genetic susceptibility traits, and aging.

PD is defined by the presence of classical hallmark motor signs - bradykinesia, rest tremor and rigidity. Postural disturbances occur usually later in the course of the disease and are no longer considered essential feature for the diagnosis. Motor signs are often preceded by non-motors features which will be discussed in detail in separate chapter. As PD progresses clinical picture becomes richer; composite of levodopa related late motor complications and non-dopaminergic features (freezing of gait, falls, non-motor symptoms - autonomic disturbances, psychiatric symptoms and dementia) develops.

In the initial stages of the disease, levodopa and dopamine agonists are effective in managing motor symptoms of the disease. Over the last decade other treatment options emerged, however levodopa has remained the most effective treatment modality of PD-related motor symptoms. As the disease progresses to late motor complication stage it is harder to pharmacologically manage these patient. Frequently existent narrow therapeutic window between off state and dyskinesias is particularly difficult to manage. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is currently recognized as standard and effective method of treatment of advanced PD.

1.2. Non Motor symptoms of PD

Underlying PD pathology involves many brain areas beyond the dopaminergic nigrostriatal system, including areas that are not directly involved in motor control, such as locus coeruleus, raphe nuclei, dorsal vagal nucleus and other ponto-medullary cell groups, the bulbus and tractus olfactorius and piriform cortex, large parts the limbic and neocortex, the diencephalon, thalamus and also extend to peripheral autonomic nervous system involving sympathetic efferents, and the myenteric plexus of the gut (Braak, Del Tredici et al. 2003, Stern, Lang et al. 2012). It is therefore not surprising that non motor symptoms form an integral part of the clinical spectrum of PD. NMS may be overlooked unless specifically looked and investigated for. 98.6% of PD patients report the presence of one or more NMS (Stern, Lang et al. 2012) and correlate with disease severity and advancing age, some however occur in early stage of the disease and may demonstrate a presenting PD symptom. NMS are a significant contributor to overall disability, increased risk for nursing home care and mortality or symptomatic orthostatic hypotension, which is one of the major risk factors of falls in PD (Chaudhuri, Healy et al. 2006).

NMS in PD involve a magnitude of functions, including sleep disturbances (e.g. nocturnal non motor symptoms, REM sleep behavioral disorder (RBD), excessive day time sleepiness), cognitive function (e.g. dysexecutive syndrome, visuospatial dysfunction, dementia, psychosis), regulation of mood (e.g. anhedonia, apathy, anxiety, depression) and hedonistic tone (e.g. dopamine dysregulation syndrome, punding), autonomic nervous system function (e.g. orthostatic hypotension, constipation, dysphagia, nausea, reduced gastric emptying and bowel movements, urogenital dysfunction, sweating), and sensory functions and pain perception (e.g. pain, paresthesia, olfactory disturbance) (Poewe Non Motor symptoms in PD, Parkinson's disease and

Movement disorders, Lippincott Williams & Wilkins, 2007). Other symptoms include fatigue, seborrhea. Weight fluctuations, notably weight loss, is a frequent non motor symptom of PD and it is regarded as heterogenous and multifactorial symptom. The pathophysiology of weight loss has not been yet fully elucidated. As weigh changes in PD are the topic of my work they are discussed in detail later in the text.

Despite the high prevalence and impact of NMS in PD, there are only few therapies available for which efficacy is sufficiently supported by evidence from randomized controlled trials in PD population. Clinical evidence indicates that dopaminergic treatment seems to be unhelpful for most of the NMS unless these are linked to motor fluctuation (wearing off related non motor symptoms such as off period pain (Chaudhuri, Healy et al. 2006).

1.3. Deep brain stimulation of the subthalamic nucleus

Surgical treatment for PD has developed from ablative procedures to implantation of electrodes into specific targets of basal ganglia. Deep brain stimulation (DBS) is currently the most frequently performed surgical procedure for the treatment of advanced PD (Fasano, Daniele et al. 2012).

The principle of stereotactic functional neurosurgery is that a structure in the brain can be accurately localized with a 3D coordinate frame that is attached to the patient's skull. The position of the target structures is determined with the use of specific landmarks in the brain (such as anterior and posterior commissures), which are visualized by MRI, CT, or by direct visualization of the target structure with MRI. For the intervention, an electrode is introduced into the target structure through a burr hole in the scull. The electrode is thin and flexible, so that it moves atraumatically with the brain. Patients are off medication the preceding night, which allows for the accentuation of both

clinical symptoms and microelectrode findings that contribute to intraoperative localization of optimal treatment electrode placement.

A combination of microelectrode recording and macroelectrode stimulation is used to refine the desired target physiologically. Once the DBS lead has been implanted, it is anchored to the skull with a burr hole cap.

The electrode is connected to an implantable pulse generator, which is the power source of the system that is generally implanted in the subclavicular region of the chest cavity. The electrode and the pulse generator are connected by an extension wire that is tunneled down the neck under the skin. The device can be programmed to deliver stimulation in monopolar or bipolar fashion, employing any of the 4 electrode contacts, alone or in combination. Stimulation amplitude, frequency, and pulse width can be adjusted to control symptoms and eliminate adverse events. The patient can turn the stimulator on or off using an Access Review Therapy Controller or a handheld magnet. The usual stimulation parameters are amplitude of 1-3 V, a frequency of 135-185 Hz, and a pulse width of 60-120 msec (http://emedicine.medscape.com/article/1965354-overview#aw2aab6b5).

The careful selection of potential DBS candidate relies on multidisplinary team efforts, usually including movement disorders expert, neuropsychologist, psychiatrist and neurosurgeon. Appropriate DBS candidate is cognitively intact patient with idiopathic PD, good response to levodopa but with motor fluctuations including shortened duration of benefit from their medication and bothersome dyskinesia despite optimal medical management. Alternatively, a patient with well-controlled PD except for medication resistant tremor may also benefit from procedure. Finally, patients with poor symptom control due to inability to tolerate adequate doses of levodopa should also be considered for

DBS (Duker and Espay 2013). Response to L Dopa remains the best predictor for surgical response, thus pre- operative evaluation of L Dopa responsiveness in mandatory, with a 33% decrease in the Unified Parkinson's disease Rating Scale (UPDRS) part III motor score is often suggested as the threshold beyond which surgical benefits materialize. Cognitive and behavioral assessments are compulsory to exclude patients with dementia and exclude patient's significant depression.

The response from DBS is only as good as the patient's best "on" time, with the exception of tremor, which may show greater improvement than is seen in medication. Daily "on" time is significantly extended after DBS.

There are different targets for DBS and with varying effects on parkinsonian symptoms; VIM DBS reduces well tremor but does not have effects on bradykinesia and other PD symptoms; STN DBS and GPi DBS have both good effects on major motor PD symptoms. The choice of the target depends on individual patient and the neurosurgeon experience. (Esselink, RAJ, Parkinson's disease related stereotactic surgery, VU University press, 2007).

Subthalamic stimulation involves implantation of the DBS lead into the subthalamic nucleus. The human STN is situated beneath the thalamus, above substantia nigra, posterior and medical to the pallidum and internal capsule, and anterior to the medial lemniscus. The rational for surgical targeting of the STN is to block the increased basal ganglia output that leads to inhibition of the thalamocortical activity and thereby alleviate the motor signs of PD (Surgical treatment of Parkinson's disease and other movement disorders, Tarsy D, Vitek JL, Lozano AM, Humana Press 2003). STN DBS is surgical procedure most commonly used to treat PD; it controls all of the cardinal PD symptoms, as well as motor fluctuations and dyskinesia. STN DBS also results in significant

reductions of antiparkinsonian medication. In the off medication condition and in comparison with preoperative scores, STN DBS significantly improved the total motor UPDRS III scores in studies with 5-10 years follow up after the surgery (Krack, Batir et al. 2003, Castrioto, Lozano et al. 2011, Rodriguez-Oroz, Moro et al. 2012). Rigidity and tremor show a stable improvement at all time points, whereas improvement in bradykinesia lasts up to 8 and 9 years (Rodriguez-Oroz, Moro et al. 2012). Gait and freezing improve up to 9-10 years, postural stability improvement is up to 5 years (Krack, Batir et al. 2003) with no amelioration in longer follow up (Castrioto, Lozano et al. 2011, Rodriguez-Oroz, Moro et al. 2012). The total UPDRS IV scores and motor fluctuations subscores improved for up 10 years in the follow up (Castrioto, Lozano et al. 2011), however there is a worsening trend in the scores over the time (Castrioto, Lozano et al. 2011). Speech and other axial symptoms tend to deteriorate in all studies (Rodriguez-Oroz, Moro et al. 2012). The reduction of L Dopa equivalent was observed up to 10 years follow up (Krack, Batir et al. 2003).

There are number of complications related to DBS, which we may divide into different categories such as surgical, hardware, stimulation related, cognitive and behavioral, risk of suicides and others.

Patient mortality from movement disorders surgery remains low and was observed 0.26%. The incidence of intracranial or intracerebral hemorrhage occurred in 2% of patients. Compared to patients with tremor or dystonia; PD patients appear to harbor increased risk of inpatient complications and hemorrhage. The modality of treatment does not affect the rates of hemorrhage (Rughani, Hodaie et al. 2013). Rughani et al also reported that hypertension, diabetes and cigarette smoking did not individually contribute to increased risk of hemorrhage, however cumulatively increasing medical comorbidities did correlate strongly with increased in- hospital complications (Rughani, Hodaie et

al. 2013). Contrary to Rughani study others reported hypertension as risk factor for hemorrhage (Binder, Rau et al. 2005, Sansur, Frysinger et al. 2007). The incidence of ischemic stroke is 0-1%, seizures in 0-3% (Follett, Weaver et al. 2010, Duker and Espay 2013, Odekerken, van Laar et al. 2013). In Follett's study; a post-operative confusional state was described in up to 21% of patients (Follett, Weaver et al. 2010). Hardware complications include lead fracture, electrode/wire replacement; devise dysfunction, infection and migration. Implantation site infection occurs in 3-8% of patients (Follett, Weaver et al. 2010, Duker and Espay 2013). Stimulation – related complications encompass paresethesia, dysarthria, and eyelid opening apraxia, hemiballismus, dizziness, dyskinesia, and facial contractions. There is a concern that DBS, particularly of the STN, may increase the risk of suicide. The prevalence of suicidal ideation may increase after DBS; multicenter study on suicide outcomes following STN DBS demonstrated a rate of 0.90% suicide attempts and 0.45% suicide completions. Attempted suicides were associated with postoperative depression, being single, having previous history of impulse control disorders or compulsive medication use, but also with younger age, younger disease onset and a previous suicide attempt (Voon, Krack et al. 2008). Data on cognitive and behavioral complications are conflicting, but most studies have reported only mild or no significant deleterious effects of STN DBS in terms of long term neuropsychological function and mood, with the exception of declines in tests of verbal fluency, working memory, and processing speed (Voon, Kubu et al. 2006, Witt, Daniels et al. 2008). Weight gain is now recognized as a frequent non motor side effect of DBS and is discussed in detail in further text.

1.4. Regulation of food intake

1.4.1. Hormones and peptides related to energy homeostasis

1.4.1.1. Peripheral orexigenic peptides

1.4.1.1.1. Ghrelin

Ghrelin is peptide hormone produced by the cells in gastric fundus; it is also expressed in duodenum, jejunum, ileum and colon; with declining concentrations from duodenum to colon (Kojima, Hosoda et al. 1999, Sato, Fukue et al. 2005). It has been suggested that ghrelin is also produced centrally by the hypothalamus (Sato, Fukue et al. 2005) and some other CNS sites, however evidence remains inconsistent and doubts exist not only regarding the ability of brain cells to produce active form of ghrelin (Abizaid 2009) but also in regards of existing production of physiologically relevant levels in CNS (Cabral, Lopez Soto et al. 2017).

Ghrelin is the only identified orexigenic gut hormone and hence the reason to be named “hunger hormone”. It is produced pre-prandially and during hunger and displays a circadian rhythm: a rise before each meal correlating with hunger scores and a rapid fall after eating with nocturnal increase. Secretion of ghrelin is controlled by many factors, such as nutrients, peptide hormones, and sympathetic nervous system (Shiimura, Ohgusu et al. 2015). Postprandial plasma ghrelin is suppressed proportional to meal calorie content in normal weight but not in obese subjects where fasting ghrelin levels have been shown to be lower compared with normal weight controls and to rise following diet induced weight loss (Cummings, 2005). Likely, brain shows increased sensitivity to ghrelin in fasting and resistance in obesity (Briggs, Enriori et al. 2010). Fasting morning ghrelin concentrations have a negative correlation with fat mass (Cummings, Weigle et al. 2002). In obese, the expected postprandial fall in circulating ghrelin levels is also attenuated , or even absent, suggesting that ghrelin is involved in pathophysiology of obesity (le Roux, Patterson et al. 2005).

The localization of ghrelin receptors on vagal afferent neurons suggest that ghrelin signals are transmitted to the brain via vagus nerve (Date, Murakami et al. 2002).

Central and peripheral administration of ghrelin stimulates food intake and body weight gain (Kojima, Hosoda et al. 1999). Ghrelin protects the organism from the consequences of negative energy balance by maintaining blood glucose levels during starvation and promoting feeding through number of pathways (Briggs and Andrews 2011).

Circulating ghrelin acts on agouti regulated peptide/neuropeptide Y (AgRP/NPY) expressing neurons in nucleus arcuatus to promote feeding. To suppress the release of anorexigenic peptides, ghrelin containing neurons send efferent fibers onto POMC neurons. There is a competitive interaction of the regulation of feeding; ARC is not only a target for ghrelin, but also for leptin. Leptin directly inhibits the appetite stimulation effects of NPY and AgRP; whereas ghrelin blocks leptin induced reduction of feeding.

Ghrelin signaling via caudal brainstem plays a role as well. Ghrelin receptors are expressed in area postrema (AP), peripheral administration of ghrelin activates AP directly and nucleus of the vagus and of the solitatory tract indirectly (Sobrino Crespo, Perianes Cachero et al. 2014).

Due to ghrelin action in extrahypothalamic pathways and more recent evidence suggests that high ghrelin levels may be a primary driver to alter the incentive salience of food and thus the motivation to work toward reinforces, in response to a high metabolic need for food (Lockie and Andrews 2013). Ghrelin may influence the rewarding properties of food through the action in ventral tegmental area (VTA) (Naleid, Grace et al. 2005), as well as modifies peripheral appetite by acting on visceral vagal afferents that ultimately modify the activity

of neurons in the dorsal vagal complex (Williams and Elmquist 2012). Ghrelin given to rats either centrally or peripherally increases their motivation to work for palatable food reinforce in a bar press task, meaning that the rats are willing to work harder for longer to obtain sucrose reinforcer (Skibicka, Hansson et al. 2012, Lockie and Andrews 2013).

Weight gain prevention through pre-prandial receptor blockage may represent the most promising role of ghrelin as a useful anti-obesity agent (Perry and Wang 2012).

1.4.1.2. Peripheral anorexigenic peptides

1.4.1.2.1. Leptin

Leptin is a peptide discovered in 1994 when the ob gene was identified and it was shown to serve as an afferent signal in negative feedback loop that maintains stability of the adipose tissue mass (Zhang, Proenca et al. 1994). Soon after the identification of leptin gene, the leptin receptor called obRb with its variant was discovered (Tartaglia, Dembski et al. 1995). Leptin is secreted mainly by adipocytes, but has been also found in the stomach and pituitary gland (Sone and Osamura 2001). Its levels are higher between midnight and early morning, perhaps suppressing appetite during the night; and likely reflecting cumulative hyperinsulinemia of the entire day (Sinha, Ohannesian et al. 1996). The production of leptin is influenced by several regulators; being stimulated by insulin and blood glucose but inhibited by sympathetic activity, lipolytic catecholamines, and free fatty acids (Sobrino Crespo, Perianes Cachero et al. 2014).

Leptin represents a major component of the physiological system that controls body weight. Leptin signals to the hypothalamus which produces a feeling of

satiety. Moreover, leptin signals may make it easier for people to resist the temptation of foods high in calories (Baicy, London et al. 2007).

Leptin serves as a major adipostat by repressing food intake and promoting energy expenditure (Rabe, Lehrke et al. 2008). Either peripheral or central administration of leptin results in reduction of food intake and body weight and increases energy expenditure (Murphy and Bloom 2004).

The effect of leptin on food intake and body weight is mediated via hypothalamic neurons (Andlin-Sobocki, Jonsson et al. 2005). Leptin is transported across the BBB via saturable mechanism via circumventricular organs – mainly the nucleus arcuatus, but also subfornical organ and area postrema. The circumventricular organs are unique due to extensive vascularization and possession of highly fenestrated capillaries. Starvation reduces transport, whereas re-feeding increases the transport across the blood brain barrier (BBB) (Sobrino Crespo, Perianes Cachero et al. 2014). In CNS leptin binds to obRp which are located within the nucleus arcuatus, however other hypothalamic nuclei such as dorsomedial, ventromedial, lateral hypothalamus and premammilary nuclei, as well as ventral tegmental area and periaqueductal grey matter also express obRp. Leptin exhibits its anorexigennic effect through leptin receptors in ARC, and furthermore inhibits orexigenic NPY/AgRP co expressing neurons and stimulates anorexigenic POMC expressing neurons in ARC (Sahu 2003).

Circulating levels positively correlate with BMI and fat tissue mass (Murphy and Bloom 2004). Although leptin reduces appetite; obese individuals generally exhibit higher circulating levels of leptin (Considine, Sinha et al. 1996). These people show resistance to leptin, similar to resistance of insulin in type 2 diabetes, with the elevated levels failing to control hunger and modulate their

weight. In many of these cases, despite high circulating levels of leptin and the presence of functional receptors, the expected anorexigenic effects of leptin are significantly diminished (Rabe, Lehrke et al. 2008). Changes in leptin signaling in ARC, change in the leptin transport over BBB or to the way leptin crosses the blood brain barrier could be another possibility contributing to leptin resistance (Myers, Cowley et al. 2008).

Additional leptin regulation of appetite and energy expenditure takes place by inhibition of serotonin synthesis and release in the brainstem neurons (Yadav, Oury et al. 2011), however some authors oppose this theory (Lam, Leinninger et al. 2011).

Low levels of leptin (and insulin) promote activation of various reward and motivational processes, signaling through both hypothalamic and VTA pathways (Cota, Barrera et al. 2006). Both leptin and insulin receptors are expressed on VTA dopaminergic neurons (Lockie and Andrews 2013).

Besides the traditional roles, leptin may be involved in other processes. Leptin receptors are expressed as well in hippocampal and glial cells (Marwarha and Ghribi 2012) and therefore leptin is thought to be a potential modulator for learning and memory processes. Recent study evaluated impact of leptin on memory function and hippocampal structure in mild cognitive impairment (MCI) and found that MCI patients have lower serum leptin. The data further suggest that inefficient leptin signaling may contribute to decreases in memory performance (Witte, Kobe et al. 2016).

1.4.1.2.2. Cholecystokinin

Cholecystokinin (CCK) is released post – prandialy by the cells of small intestine. CCK mediates satiety by acting on the CCK receptors within CNS mainly in area postrema, nucleus tractus solitarius and dorsomedial hypothalamus. CCK has

been also shown to interact with orexins, which are involved in feeding behavior (Tsujino and Sakurai 2009). It is predominantly synthesized and released from the duodenum and jejunum. The mechanism of action of CCK is a rapid inhibition of hunger after meal. The mechanism for this hunger suppression is thought to be a stimulation of gallbladder contractions and decrease in the rate of gastric emptying (Lamers, Lieverse et al. 1995, Dufresne, Seva et al. 2006).

1.4.1.2.3. Insulin

Insulin is produced by be cells of the pancreas and it is a signal of satiety and obesity. Insulin enters the brain mainly via ARC crossing the BBB by saturable mechanism and reduces energy intake. Reduced expression or deletion of insulin receptors in the brain leads to hyperfagia and obesity (Schwartz and Porte 2005). Insulin receptors are highly expressed in POMC/CART and NPY/AgRP neurons. Insulin and leptin both activate POMC neurons, insulin stimulating the synthesis of AgRP. Insulin deficiency is associated with increased NPY, while insulin administration inhibits hypothalamic NPY expression (Sobrino Crespo, Perianes Cachero et al. 2014). Central action of insulin promotes anorexia because it decreases NPY and stimulates POMC expression (Banks 2008).

Further anorectic peptides have been identified: glucagon like peptides, peptide tyrosine tyrosine, pancreatic polypeptide, amylin, oxyntomodulin, bombesin and obestatin.

1.4.1.3. Central hypothalamic peptides

1.4.1.3.1. Hypothalamic orexigenic peptides

1.4.1.3.1.1. Orexins

Orexins, also known as hypocretin neurons are known to play crucial role in the regulation of sleep/wake cycle, feeding behavior, emotions, autonomic nerve activity, whole-body energy metabolism and central regulation of glucose homeostasis (Girault, Yi et al. 2012, Tsuneki, Wada et al. 2012). They are located in the lateral hypothalamic area, perifornical area and posterior hypothalamus. Orexin receptors are abundant in ventromedial hypothalamic nucleus (orexin-1-receptor) and tuberomammilary nucleus, paraventricular nucleus, ARC and LHA including perifornical area (orexin-2-receptors). Leptin and glucose inhibit their activity, whereas increased ghrelin is stimulatory (Yamanaka, Beuckmann et al. 2003).Orexin neurons primarily implicated in reward seeking behavior project from lateral hypothalamus to many areas of the mesolimbic reward pathway including VTA and nucleus accumbens (Baimel and Borgland 2017). As orexin containing neurons are firmly established as regulators of reward seeking (Baimel and Borgland 2017) they are able to monitor humoral and neural indicators of energy balance and mediate adaptive augmentation of arousal in response to fasting (Tsujino and Sakurai 2009), but also receive information about body's energy status via signals from ARC NPY and POMC neurons (Elias, Saper et al. 1998). Functional studies indicate that synaptic plasticity of LHA orexin neurons is one of the key mechanisms used by these neurons in regulating arousal and energy metabolism, because overnight food deprivation in rodents (i.e., fasting; rodents are nocturnal animals) promotes the formation of more excitatory synapses onto LH orexin neurons, whereas this is reversed by refeeding (Horvath and Gao 2005). It has been hypothesized that orexin neurons play key role in the generation of hunger – induced wakefulness and also in after meal sleepiness (Burdakov and Alexopoulos 2005).

1.4.1.3.1.2. Neuropeptide Y (NPY)

NPY is strong stimulator of feeding. It is synthetized by neurons in nucleus arcuatus, which project mainly to PVN, dorsomedial, and lateral hypothalamus. Research suggests that NPY also regulates hedonic aspects of feeding through its projections to the brain reward circuitry (ventral tegmental area, lateral hypothalamus, nucleus accumbens (Pandit, la Fleur et al. 2013).

Leptin and insulin inhibit production and release of NPY, glucocorticoids on contrary stimulate.

Additional orexigenic peptides include AgRp, MCH, galanince, galanine like peptide, cerebellin 1 (Sobrino Crespo, Perianes Cachero et al. 2014).

1.4.1.3.2. Hypothalamic anorexigenic peptides

1.4.1.3.2.1. Corticotropin releasing hormone (CRH)

CRH is major physiological regulator of pituitary ACTH secretion and is produced by neurons in PVN. When centrally injected, CRH inhibits food intake and reduces body weight in rats. Peripheral administration increases energy expenditure and fat oxidation in humans. Leptin and cortisol show inverse circadian rhythm, therefore it is suggested that a regulatory feedback is present. Leptin stimulates CRH expression, while pre-treatment with CRH antagonists attenuates the leptin induced reduction of food intake and body weight (Sobrino Crespo, Perianes Cachero et al. 2014).

Glucocorticoids act directly on the adipose tissue and increase leptin synthesis and secretion in humans. They appear to act as a key modulator of body weight and food intake, promoting leptin secretion by adipocytes, limiting central leptin induced effects and favoring those of the NPY. Glucocorticoids have been implicated in body weight regulation and in the pathogenesis of obesity through its orexigenic and adipogenic effects or its counter regulatory effect against insulin, such as gluconeogenesis and impaired glucose uptake (Leal-Cerro, Soto

et al. 2001). There is a neuroendocrine integration of the stress centers in the CNS with centers that control appetite. Acute stress exerts anorexigenic effect through stimulation of POMC/CART neurons by increased CRH levels and an additional decrease of NPY secretion (Kyrou, Chrousos et al. 2006). In acute stress CRH activates the hypothalamic pituitary adrenal axis leading to an increase in cortisol secretion with in turn inhibits the activation of the HPA axis. In chronic stress, the elevated glucocorticoids exert orexigenic effects caused by the inhibition of CRH and stimulation of NPY expression (Kyrou, Chrousos et al. 2006) leading to increase in body weight.

1.4.1.3.2.2. Melanocortins and Cocain amphetamine related transcript (CART)

CART is powerful anorexigennic neuropeptid and CART expressing neurons occur mainly in PVN, dorsomedial and lateral nucleus, perifornical regions and ARC.

The melanocortins are posttranslational products of the proopiomelanocortin (POMC) prohormone. There are multiple forms of melanocortin family, but it is the melanocyte stimulating hormone (MSH) is presumed to be the most relevant melanocortin involved in energy regulation within the hypothalamus (Gantz and Fong 2003).

1.4.1.4. Other

For the completeness adiponectin and resistin will be discussed as well.

1.4.1.4.1. Adiponectin

Adiponectin is a protein synthetised mainly by white fat tissue. Adiponectin has been postulated to play an important role in the modulation of glucose and lipid metabolism in insulin sensitive tissue. Contrary to other adipokines, adiponectin levels rise with a reduction in fat mass and is decreased in obesity. An inverse relationship to glucose and insulin exist (Kadowaki and Yamauchi 2005). Decreased circulating adiponectin levels have been demonstrated in genetic and

diet induced murine models of obesity and well as in diet induced forms of human obesity; and in type 2 diabetes mellitus (Schulz, Paulus et al. 2010). Antiatherogenic effects of adiponectin have been described as well (Diez and Iglesias 2003).

Contrary to leptin, the role of adiponectin in the brain has not yet been well elucidated (Schulz, Paulus et al. 2010). It has been initially suggested that adiponectin was not present in the brain as it was unable to cross the blood brain barrier, but in 2007 Kubota and al demonstrated that peripherally administered adiponectin stimulated AMPK in the hypothalamus of the mice to increase food intake and decrease energy expenditure (Kubota, Yano et al. 2007).

There is substantial evidence to suggest that adiponectin receptors are widely expressed in the human brain in the areas of hypothalamus, brainstem, cortex, pituitary gland and hipocampus (Kubota, Yano et al. 2007, Thundyil, Pavlovski et al. 2012), however it is still not clarified if CSF adiponectin is produced and how it circulates in the brain. There are two forms of adiponectin receptors, AdipoR1 and AdipoR2 that are expressed in CNS with more pronounced expression AdipoR1 but also other tissues (Ebinuma, Miida et al. 2007, Thundyil, Pavlovski et al. 2012). AdipoR1 and AdipoR2 are present in both POMC/CART and NPY/AgRp neurons (Guillod-Maximin, Roy et al. 2009). Also co-localization of the AdipoR1 and obRb in the nucleus arcuatus of mice was discovered. Only the low molecular weight adiponectin hexamers have been detected in CSF (Kubota at all 2007) but the issue of adiponectin transport from the periphery into the CNS and how this occurs remains is a matter of discussions and more work is required for clarification. There are some works supporting production of low molecular weight hexamers adiponectin in CNS in animals (Wilkinson 2007), but also in humans in studies with patients with polycystic ovaria (Glintborg, Frystyk et al. 2008). It appears, that while adiponectin's peripheral effects are mediated

predominantly by HMW forms, LMW multimers may be responsible for its central effect (Thundyil, Pavlovski et al. 2012). If transport across BBB exists, it is likely that adiponectin enters the brain via receptor mediated transcytosis or via circumventricular organ (Schulz, Paulus et al. 2010).

Inverse relation of plasma leptin and adiponectin levels with that of body weight led to hypothesis that adiponectin could exert a central control of energy homeostastis. This speculation led to various studies that suggested that adiponectin reduced food intake. Kubota demonstrated that peripherally administered adiponectin rather exerted an orexigenic effect and decreased energy expenditure (Kubota, Yano et al. 2007). Based on those results there is strong evidence that adiponectin plays a crucial role in physiological neuromodulation of food intake, energy expenditure and possible even neuroendocrine and autonomic functions in the brain.

1.4.1.4.2. Resistin

Based on rodent studies; resistin was primarily thought to be produced in humans by adipocytes indicating link between obesity and insulin resistance (Steppan, Bailey et al. 2001). Later works showed that human resistin is predominantly secreted by macrophages (Patel, Buckels et al. 2003) suggesting that resistin is linked to inflammation (Lehrke, Reilly et al. 2004). Obese individuals have a greater infiltration of macrophages in adipose tissue; show increased expression of resistin in fat tissue and have higher circulating levels of resistin than in lean individuals.

Conflicting results are published regarding human resistin and its association with parameters of obesity or insulin resistance; however it seems that there is an association between resistin levels and visceral fat (Jain, Massaro et al. 2009). Resistin likely plays an important role in pathogenesis and progression of atherosclerosis in humans (Park and Ahima 2013).

1.4.2. Food intake and energy metabolism regulation

The regulation of feeding, energy intake and expenditure, and body weight is a homeostatic process (Wilding 2002). Because of its biological importance, food intake and energy expenditure are controlled by complex, redundant, but extremely reliable, distributed neural systems that reflect the fundamental biological importance of adequate nutrient supply and energy balance (Lenard and Berthoud 2008), Figure 1. While hypothalamus and caudal brainstem play crucial roles in this homeostatic function, areas in the cortex and limbic system are important for processing information regarding prior experience with food, reward, and emotion, as well as social and environmental context (Berthoud and Morrison 2008).

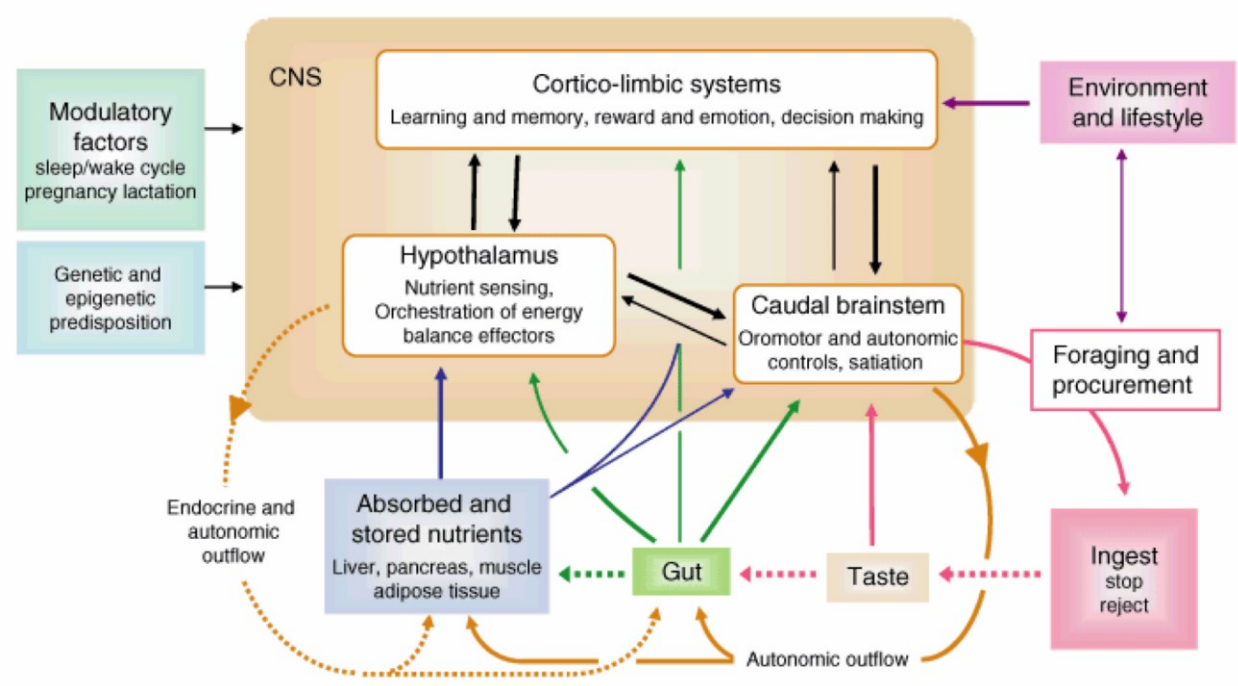


Figure 1. Highly schematic diagram showing major components and flow of information of the peripheral and central systems involved in energy balance, regulation, and control of food intake (Lenard and Berthoud 2008)

Once food passes into the GI tract, it is processed and absorbed into the blood stream. Gut has different types of chemoreceptors and mechanoreceptors from which the information reaches the brain via vagal nerve. Vagal nerve sensory

information has been linked to process of satiety and meal termination (Berthoud, Munzberg et al. 2017). The gut as the largest endocrine organ produces a numerous peptides in response to food within the GI system and these interact with receptors at various levels of the “gut-brain axis” to affect short term and intermediate term feelings of hunger and satiety (De Silva and Bloom 2012) and to alter feeding behavior (Berthoud, Munzberg et al. 2017).

Ghrelin produced by empty stomach has stimulatory effect on appetite and is one of the main signals of short term regulation which determines the beginning and the end of a meal (hunger and satiation) (Abdalla 2017) . The effect is mediated via inhibition of vagal afferents (Cummings, Purnell et al. 2001). On contrary, leptin, an adipose tissue hormone, acts as long term adiposity signal, suppresses food intake and informs the brain of energy stores in the body.

Besides the vagal afferents number of nutrients, hormones and cytokines reach the brain directly via weak blood brain barrier or via transport mechanisms (Berthoud and Morrison 2008, Berthoud, Munzberg et al. 2017).

Within the brainstem, it is the dorsal vagal complex (DVC) which is critical in the interpretation and conveying the information from peripheral signals into the hypothalamus. Receptors for variety of peptides controlling food intake have been found to be expressed in the brainstem vagal afferent neurons (Abdalla 2017).

Hypothalamus plays a major role in the control of appetite and food regulation in general. The integration of the information occurs mainly at nucleus arcuatus, but also paraventricular nucleus, dorsomedial nucleus, lateral hypothalamic area and ventromedial hypothalamic nucleus are involved.

There are two distinctive populations of hormones within the ARC, with opposing effect on food intake; one expressing the anorexigennic peptides propiomelanocortin (POMC) and cocain – and amphetamine –regulated transcript (CART), and thus suppressing food intake; and the other expressing orexigennic food intake stimulating NPY and AgRP peptides. Both populations are sensitive to leptin, insulin, ghrelin, insulin and other metabolites and peptides. Figure 2 outlines regulation of food intake at the level of ARC nucleus.

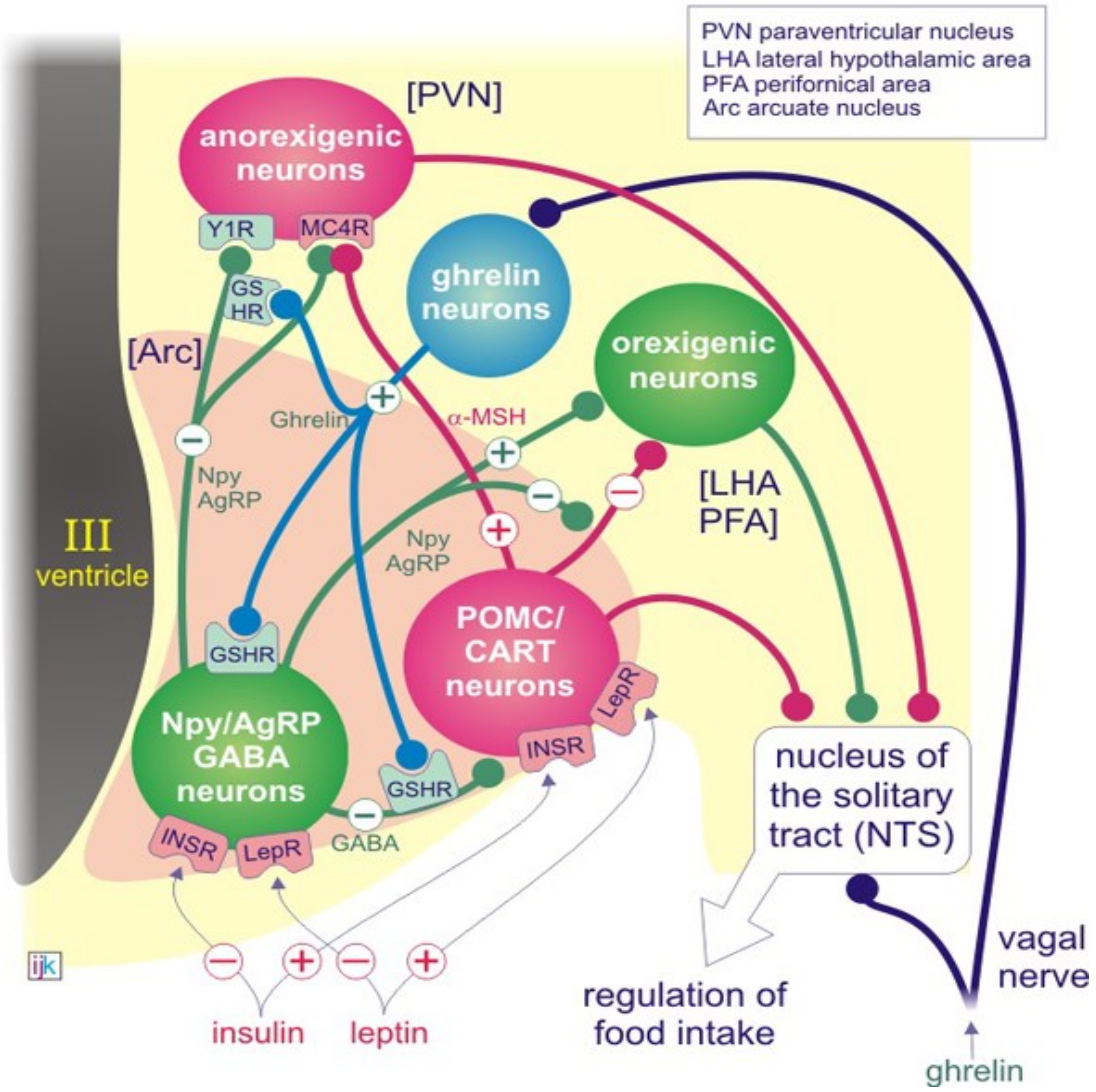


Figure 2. Regulation of food intake at the level of the arcuate nucleus (ventro-medial hypothalamus) (http://www.cellbiol.net/ste/alpobesity2.php)

1. The orexigenic message of ghrelin enters the brain via the vagus nerve and binds to its receptor on Npy/AgRP/GABA neurons, giving rise to an increased production of Npy and AgRP as well as an increased firing rate of these neurons. The consequences are twofold: firstly, inhibition of firing of

POMC/CART neurons (through GABA) and secondly stimulation of firing of the orexigenic neurons in the LHA/PFA region (through Npy and AgRP). A predominant orexigenic signal ensues.

2. Insulin and leptin directly diffuse into the arcuate nucleus and they bind to their receptors on both Npy/AgRP/GABA and POMC/CART neurons. However, they have opposing effects on these neurons. Leptin and insulin promote expression of α-MSH (anorexigenic) but suppress expression of Npy and AgRP (orexigenic). As a consequence a predominant anorexigenic signal ensues.

Both NPY/AgRP and POMC/CART neurons project to the paraventricular nucleus, dorsomedial nucleus, lateral hypothalamic area and ventromedial hypothalamic nucleus.

PVN contains neuronal populations which receive direct input from NPY and POMC neurons. These produce anorexigenic peptides such as CRH, thyreotropine releasing hormone (TRH) and oxytocin and are involved in autonomic and neuroendocrine functions including the regulation of HPA axis. The produced substances negatively influence food intake and increase metabolic rate.

The LHA contains orexigenic hormones orexins and melanin-concentrating hormone which receive metabolic input and enhance food intake. In the LHA there is as well neuronal population expressing leptin and some demonstrate sensitivity to glucose. Besides the metabolic input, the LH neurons receive information from brain areas associated with reward, motivation and memory (Lenard and Berthoud 2008) and sensory inputs from the brainstem areas which receive information mainly via vagal nerve (Cummings, Purnell et al. 2001, Naleid, Grace et al. 2005). LH sends abundant outputs to numerous areas of the brain and spinal cord. *Figure 3 schematically describes hypothalamic regulation of food intake and its extensive connections to other brain areas*

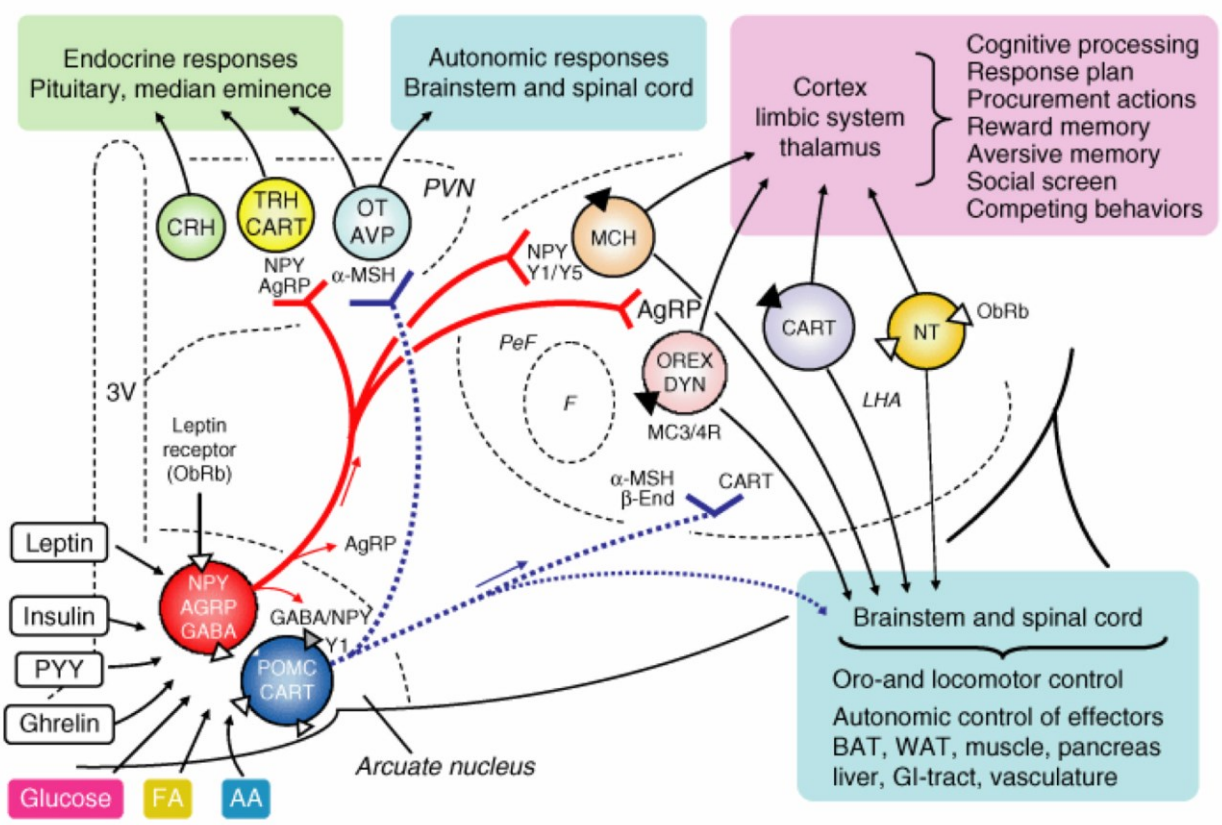


Figure 3. Diagram showing the two known neuron populations in the arcuate nucleus sensitive to signals of fuel availability and their projections to other key neuron populations orchestrating the adaptive behavioral, autonomic, and endocrine responses(Lenard and Berthoud 2008).

CART, cocaine- and amphetamineregulated transcript; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; MCH, melanin concentrating hormone; α-MSH, α-melanocyte-stimulating hormone; PVN, paraventricular nucleus.

Other hypothalamic structures are also involved, the VMN receives NPY, AgRP and POMC neuronal projections from ARC and expresses large population of glucosensitive neurons as well as the brain derived neurotrophic factor (BDNF) neurons which are activated to decrease food intake, the DMN receives NPY/AgRP and MCH projections from ARC (Abdalla 2017).

Based on the above it is clear that the proper regulation of energy balance requires complex and coordinated effort of many hormones, peptides, neurotransmitters as well as multiple brain areas and nuclei. Figure 4 presents short term regulation of food feeding behavior. If an organism presents energy deficit the brain is informed via increased levels of ghrelin and drop

in leptin levels and other gut hormones which leads to activation of NPY/AgRP neurons and inhibition of POMC neurons. Subsequently search for food begins with ghrelin facilitating retrieval of memory traces of former experience with food and loading the appropriate spatial maps into hippocampus. Arousal system and orexins become activated to strengthen sympathetic tone of muscle and heart and sharpen the external senses. The combination of high ghrelin and low leptin sensitizes the mesolimbic system to start searching for the food. The parasympatic system gets ready to prepare GIT for the incoming food. Once it is eaten, ghrelin level dramatically drops and leptin on contrary rises. When satiety occurs, the orexigenic and arousal system turns off (Lenard and Berthoud 2008).

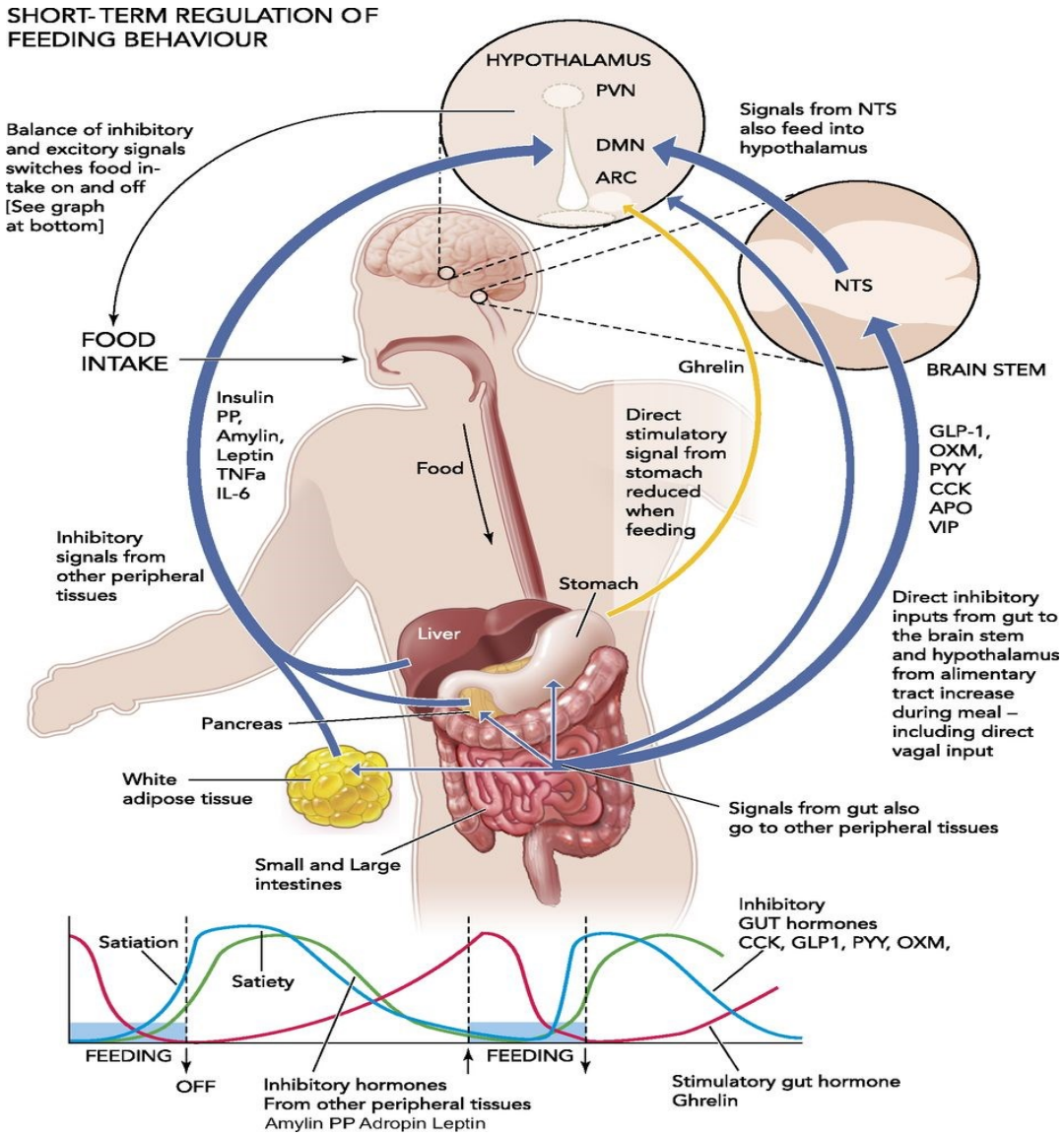


Figure 4: Short term regulation of feeding behavior (http://physiologyonline.physiology.org/content/29/2/88.figures-only)

Hedonic involvement is mentioned multiple times in the above text, reward system interacts with homeostatic controls to regulate body weight; different brain circuits involved in reward system are activated by food and food related cues (Abdalla 2017).

1.5. Weight changes in Parkinson disease

1.5.1. Anthropometric parameters

Most of the patients with PD experience weight loss ((Abbott, Cox et al. 1992, Durrieu, Llau et al. 1992, Markus, Tomkins et al. 1993, Davies, King et al. 1994), Beyer, Palarino et al. (1995), (Kashihara 2006, Cumming, Macleod et al. 2017). The frequency of weight loss is quite high; unintended weight loss was reported in 52% of PD patients (Abbott, Cox et al. 1992). Weight loss in PD may begin 2–4 years before the diagnosis is made (Chen, Zhang et al. 2003). It may be predominant in women than in man (Durrieu, Llau et al. 1992) and becomes marked in patients with advanced disease (Markus, Tomkins et al. 1993, Uc, Struck et al. 2006). Interestingly, couple studies reporting overweight PD patients were also published (Morales-Briceno, Cervantes-Arriaga et al. 2012, Vikdahl, Carlsson et al. 2014) and recent study reported malnutrition in PD patients in the absence of weight loss (Lindskov, Sjoberg et al. 2016).

Controversial studies exist on BMI relationship and PD; however published meta-analysis on BMI in PD reported a lower BMI in PD patients compared to controls, which was only related to disease severity and not to disease stage (van der Marck, Dicke et al. 2012). Interestingly BMI is reduced in early pre-symptomatic PD (Cheshire and Wszolek 2005) which is corresponding to the reported weight loss in early PD (Chen, Zhang et al. 2003).

The reduction of measured anthropometric parameters is related most to skin fold thickness which is indicator of percentage of body fat and therefore suggests that weight loss in PD is primarily due to loss of fat mass rather than muscle loss (Abbott, Cox et al. 1992, Markus, Tomkins et al. 1993). Recent study investigated among others mid upper arm muscle circumference and handgrip

strength and found decrease in both parameters discussing possible development of sarcopenia in PD patients (Lindskov, Sjoberg et al. 2016).

The prevalence of malnutrition, defined as protein – energy undernutrition in people with Parkinson's disease is reported from 0% to 24%, while 3-60% of PD patients were reported to be at risk of malnutrition (Barichella, Villa et al. 2008, Sheard, Ash et al. 2011, Sheard, Ash et al. 2013, Lindskov, Sjoberg et al. 2016). Most of the studies included mobile patients without cognitive impairment, therefore it is likely that the frequency of malnutrition in PD patients is underreported (Sheard, Ash et al. 2011). Food habits and intake of nutrients demonstrated that PD patients tend to decrease their intakes of high quality snacks and their prepared complete meals, those with weigh loss also increase their daily intakes of fat and their energy intake per kg body weight (Lorefalt, Toss et al. 2009).

1.5.2. Mechanisms of PD weight loss

The mechanism of weight loss in PD is still not fully elucidated; a number of factors have been proposed as contributing to weight loss such as presence of dyskinesia (Markus, Tomkins et al. 1993), disease severity (Markus, Tomkins et al. 1993, Beyer, Palarino et al. 1995) and female sex (Durrieu, Llau et al. 1992, Lorefalt, Toss et al. 2009). Other factors are increased metabolic rate, increased energy expenditure, levodopa therapy, autonomic dysfunction, impaired intestinal motility and impaired swallowing (Sharma and Turton 2012), hedonic abnormalities. Recent publication looked at effect of different covariates and found that higher age, baseline weight, female gender, higher baseline UPDRS scores, greater postural instability, difficulty eating and drinking , lower cognitive scores and baseline levodopa use were all associated with weight loss

(Wills, Li et al. 2017). Following text is focused on potential contributors to weigh loss.

Inadequate energy intake in patient with PD

One reason for unintended weight loss starting from the beginning of PD may be worsened exploitation of energy due to gastrointestinal visceromotor impairment. Also olfactory dysfunction together with motor disability can lead to decreased appetite and inadequate energy intake.

Olfaction in PD

Olfactory dysfunction in PD has been known for many years, first reports are dated nearly 40 years ago (Ansari and Johnson 1975). Olfactory impairment may contribute to anorexia and reduced appetite in PD patients (Wszolek and Markopoulou 1998) and thus be one of the factors leading to weight loss. Sharma and colleagues studied a relationship between olfaction and body weight profile in PD (Sharma and Turton 2012) and found that PD patients which lost weight had more severe impairment of olfaction. According to Braak pathological classification (Braak, Del Tredici et al. 2003) impairment of olfaction is developed in prodromal phase of PD when both the anterior olfactory nucleus and the tract are affected and show alfa – synuclein aggregates. The degree of olfactory dysfunction varies from anosmia to different degrees of hyposmia. First studies reported no correlation between this non motor symptom and severity of PD patients studied (Ward, Hess et al. 1983), another study (Sharma and Turton 2012) however revealed significant reduction of olfaction with progression of PD in weight loss patients and interestingly report that weight loss preceded onset of dyskinesia. This study identified two phenotypes of PD based on the degree of olfactory dysfunction: anosmic group – group with higher initial body weight, weight loss as the disease progresses and higher risk

of dyskinesia and hyposmic group with lower initial body weight that does not lose or even gain weight as the disease progresses and is at lower risk of dyskinesia. Possible explanation is that the patients with anosmia have a higher and probably faster progression of neurodegeneration than hyposmic patients or that the neurodegeration in anosmic subjects has been going on for longer duration (Lewy body infiltration in olfactory tissues).

Gastrointestinal tract dysfunction (GIT) in PD

GIT dysfunction stands among the most common non – motor symptoms of PD. Symptoms such as dysphagia, nausea, gastroparesis, and bowel dysfunction, including both reduced bowel movement frequency and dyschesia, are significant cause of disability in these patients (Pfeiffer 2011). Impaired motility and absorption from GIT may produce weight loss and may also cause erratic absorption of levodopa and dopamine agonists. Further anti- parkinsonian medication, including anticholinergic agents, may further aggravate bowel dysfunction. The underlining neurodegenerative mechanism is still not clear. Dopaminergic deficiency secondary to nigrostrital damage may be responsible for some aspects of GI dysfunction in PD, it is also clear that additional sites both in the central and peripheral nervous system are involved. Some of the brainstem nuclei such as the dorsal motor nuclei of the vagus, which provides parasympathetic innervations of large part of GI, are profoundly involved in PD. Enteric nervous system (ENS) pathology is widely present; in PD, the enteral system is affected by alfa synucleinopathy; Lewy bodies within the ENS were firstly reported already in 1984 by Qualman (Qualman, Haupt et al. 1984). Braak suggests that alfa synuclein depositions within stomach ENS may be the earliest site of pathology in PD, beginning in pre- motor stages of the disease (Braak, de Vos et al. 2006).

Functional impairment during swallowing is present in 75-97% of PD individuals (Bushmann, Dobmeyer et al. 1989, Fuh, Lee et al. 1997, Leopold and Kagel 1997) and all stages of swallowing may be affected in PD. Various investigations have detected functional alteration of both oropharyngeal and oesophageal motility in about 60-80%, but such alterations may be asymptomatic (Natale, Pasquali et al. 2008). Dysphagia may be for both solids and liquids. Dysphagia as an early sign of PD has been historically controversial; some suggesting that dysphasia may be present early in the course of the disease (Potulska, Friedman et al. 2003), while others considered dysphagia occurrence within the first year of symptom onset as "red flag" indicating the diagnosis of Parkinson plus syndrome. Also Jankovic et al who compared BMIs of patients with PD and progressive supranuclear palsy found no differences in BMI between the two groups, but dysphagia predominated in PSP (Jankovic, Wooten et al. 1992). Recent evidence however confirms that dysphasia is indeed an early sign of PD (Wang, Shieh et al. 2017, Pflug, Bihler et al. 2018).

Impaired or delayed gastric emptying is the cause of nausea frequently seen in PD. Most commonly, nausea is due to dopaminergic antiparkinsonian medication, although it might be also present in non-treated PD patients (Edwards, Pfeiffer et al. 1991).

PD patients than suffer from early satiety, nausea and sense of bloating which is may be caused by gastroparesis (Goetze, Nikodem et al. 2006). Gastroparesis is characterized by impaired gastric emptying and intestinal dysmobility.

Constipation defined as decreased bowel movement frequency of less than three bowel movements per week is the most commonly reported gastrointestinal symptom of PD affecting up to 89 % of patients (Cersosimo and Benarroch 2012). The pathophysiological mechanism includes impairment of

colonic motility which is likely to be contributed to Lewy pathology within GI tract and sympathetic network within submucosal colonic plexus (Lebouvier, Neunlist et al. 2010) and has been speculated to be a premotor and early stage of PD. The severity of constipation correlates with disease severity, but slowed colon transit is very likely present already in early untreated PD (Jost and Schrank 1998) and even may precede the development of motor dysfunction in PD (Abbott, Petrovitch et al. 2001). Pagano et al confirmed that the constipation in early drug naïve patients was not associated with dopamine transporter pathology but with rapid eye movement sleep behavior disorder and depression, which are both speculated to be a pre motor symptom of PD (Pagano, Yousaf et al. 2018).

Lewy neuritis (LN) in submucosal plexus was found in 72% of patients with a strong correlation between LN burden and disease severity and UPDRS III axial score and negative correlation of levodopa responsiveness and severity of pathological burden (Lebouvier, Neunlist et al. 2010). No correlation was found between pathology and disease duration (Lebouvier, Neunlist et al. 2010).

Increased energy expenditure

The literature sources describing resting metabolism and energy expenditure in PD patients vary. Despite eventual weight loss, PD patients increase their energy intake by about 350 kcal/day, mainly due to increased carbohydrate intake (Davies, King et al. 1994, Chen, Zhang et al. 2003). This suggests that weigh loss in PD is due to increase energy expenditure. Indeed, Marcus and Levi found resting energy expenditure (REE) to be elevated in PD patients (Levi, Cox et al. 1990, Markus, Cox et al. 1992). Marcus also described increased REE in both treated and untreated patients in the absence of dyskinesias; the largest difference was found between the two states at patients who developed

marked muscle rigidity in the untreated state. The result suggested for the first time that rigidity might be important cause of raised EE and also of weight loss in PD. Levi et al also examined patients EE before and after medication and concluded that EE did not change in subject with no clinical change, was reduced in those whose rigidity was decreased and was increased in patients with involuntary movements (Levi, Cox et al. 1990).

Contrary results reported no difference in resting metabolism between PD patients and healthy age matched controls. Free living energy expenditure was lower due to decreased physical activity energy expenditure which was attributed to reduction in purposeful physical activity (Toth, Fishman et al. 1997).

When investigating energy expenditure comparing PD patients with stable weight and PD patients with weight loss and found no difference in daily energy expenditure (DEE), REE, in caloric intake (Delikanaki-Skaribas, Trail et al. 2009) between the groups suggesting that weight loss cannot be fully elucidated by elevated energy expenditure and negative daily balance. Interestingly the caloric intake was higher in PD patients losing weight when expressed in kg per body weight, which could be explained either by worsened absorption in GIT or patients underreporting energy intake.

Capecci and colleagues confirm the increased REE in PD patients correlating with disease duration in and rigidity but only in OFF state (Capecci, Petrelli et al. 2013).

Only one publication evaluates energy expenditure in PD patients after STN DBS at month 3 and 12 months post-surgery finding not significant changes in REE pre and post operatively (both in Med OFF and STIM OFF and MED OFF and STIM ON) and significant decrease in total energy expenditure after surgery with concomitant decrease in energy intake. The patients however remained in positive energy balance during the study which provides evidence for

insufficient decrease in energy intake in studied patients (Jorgensen, Werdelin et al. 2012).

L Dopa and body changes

The role of L-dopa and other dopaminergic medication in changes of body weight in PD patients is still not fully understood. Simple explanation may be that dyskinesias induced by L-dopa treatment increase energy metabolism which subsequently leads to weigh loss, however PD energy metabolism studies conclude conflicting results.

Metabolic changes in long term L-dopa treatment are hypersecretion of both insulin and growth hormone and an increase in concentration of free fatty acids (Boyd, Lebovitz et al. 1970, Sirtori, Bolme et al. 1972). Such hormonal derangement can trigger a lipolytic cycle that is thought to be responsible for the increase in basal metabolic rate and weight loss. Disruption of this derangement due to neurosurgical procedures or L-dopa dosage reduction could explain weigh gain. Palhagen and his team as corroborated the hypothesis that PD meds may directly affect adipose tissue. He found that weight loss in PD patients is more prominent after L-dopa initiation and continues to decrease during further L-dopa treatment and based on the results hypothesized that L-dopa treatment per se could contribute to weight loss (Palhagen, Lorefalt et al. 2005). Higher rate of levodopa use in patients who lost weight was also found by Akbar and colleagues (Akbar, He et al. 2015). German study reported the L-dopa dosage per kg body weight, the total L-dopa equivalent dosage per kg body weight and the total dopaminergic medication per kg body weight show an inverse correlation with the BMI pointing to a dose dependent L-dopa associated weight loss (Bachmann, Zapf et al. 2009).

Conflicting results are however available as well. Adams found that L-dopa/carbidopa caused a switch from lipid to carbohydrate metabolism and more over in adipose tissue, levodopa benserazid appears to attenuate lipolysis through direct antilipolytic actions, thus not supporting levodopa/benserazide per se contributes to body fat loss in this patient population (Adams, Boschmann et al. 2008).

Serotonergic dysfunction

Serotonin is involved in eating behavior promoting proper energy balance and high cerebral levels improve mood, depression, and sleep (Tecott, Sun et al. 1995). Serotonergic terminals converge on the arcuate nucleus which is supportive of and endogenous role of serotonin similar to leptin; stimulating POMC and inhibiting NPY neurons (Heisler, Jobst et al. 2006). Serotonergic system as well is affected by alpha synuclenopathy (Goedert, Spillantini et al. 2013). Serotonergic dysfunction plays role in a number of parkinsonian symptoms, including motor function, L Dopa induced dyskinesia, mood, psychosis, constipation (Fox, Chuang et al. 2009), fatigue, weight and appetite problems (Politis, Loane et al. 2011). Based on the results of study investigating relationship between BMI changes and serotonergic dysfunction in PD patients it is suggested that lower levels of 5-HT resulting from and increased clearance in the synapse could play a role in the pathophysiology of fluctuating BMI in PD (Politis, Loane et al. 2011). Neurodegeneration of the serotonergic system with low level of serotonin in PD may also explain the pronounced preference for all kinds of sweets and increased intake of chocolate in PD patients (Wolz, Kaminsky et al. 2009).

Impaired homeostatic regulation of energy metabolism

In view of the fact that weigh loss in PD occurs before the onset of motor symptoms, and remaining unclarity on the pathophysiological mechanisms of weigh changes in PD, it was hypothesized that homeostatic regulation of energy metabolism may be disrupted. Currently it has been found that neurons producing orexins are massively lost in PD (Drouot, Moutereau et al. 2003), ghrelin levels are reduced (Unger, Moller et al. 2011).

Hedonic system dysregulation

As eating behavior is also regulated by hedonic factors, decreased rewarding in dopaminergic mesolimbic system found in PD likely contributes to weight loss in these patient population. Figure 5 shows feeding behavior regulatory mechanisms and their dysregulation in Parkinson's disease (De Pablo-Fernandez, Breen et al. 2017).

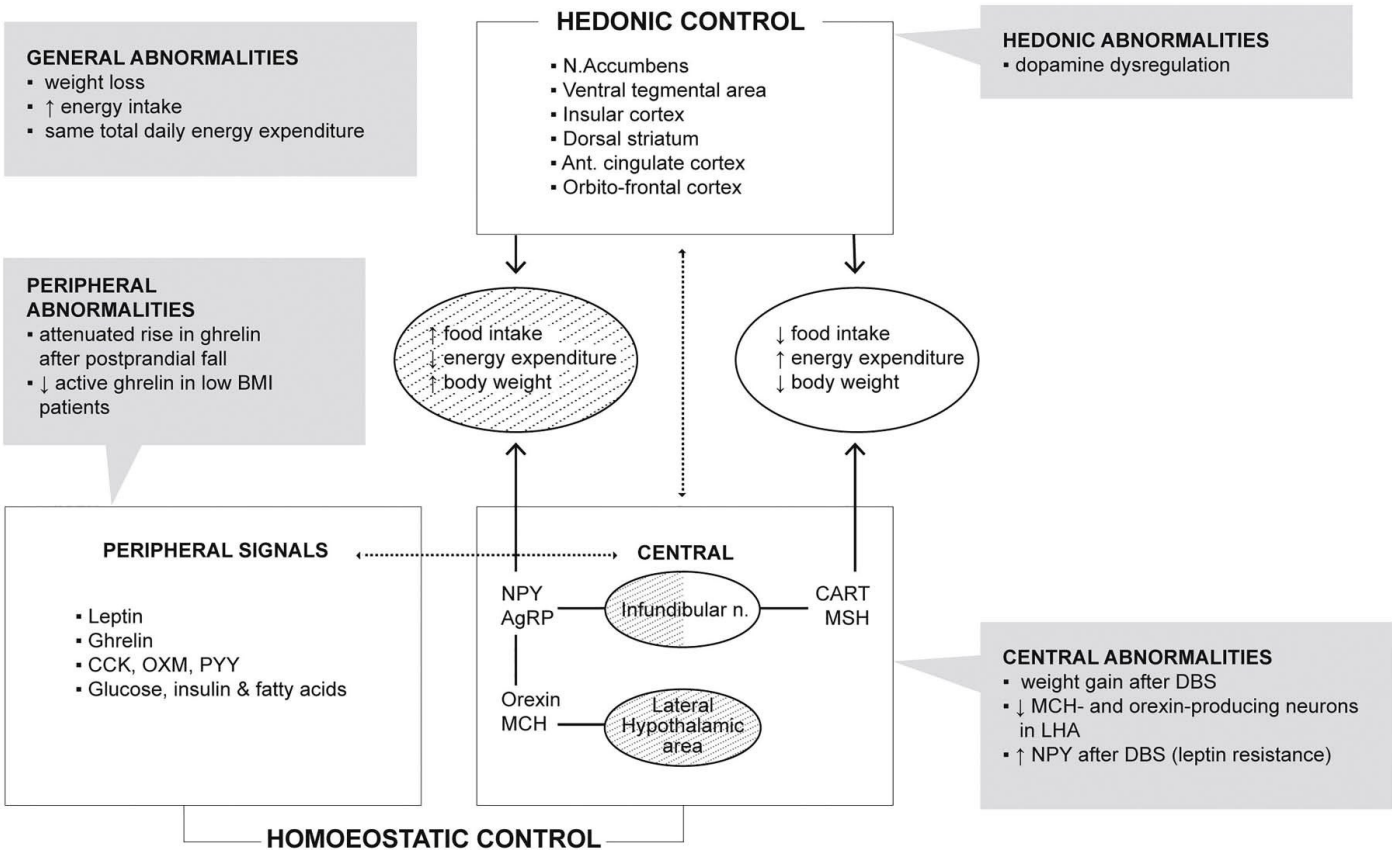


Figure 5: Feeding behavior regulatory mechanisms and their dysregulation in PD. (De Pablo-Fernandez, Breen et al. 2017)

1.5.3. Food related parameters and energy metabolism factors in PD

Adipokines are strongly associated with weight changes and therefore it was of interest to evaluate whether weight loss in PD patients may be connected to adipokines alterations. Leptin, as a signal of satiety, brought most attention. Lower leptin levels were found in PD patients with unintended weigh loss (Evidente, Caviness et al. 2001, Fiszer, Michalowska et al. 2010). As expected, leptin correlated positively with BMI (Lorefalt, Toss et al. 2009, Fiszer, Michalowska et al. 2010, Rocha, Scalzo et al. 2014) and its PD levels were comparable to leptin concentrations of controls matched by age and BMI (Lorefalt, Toss et al. 2009, Fiszer, Michalowska et al. 2010, Rocha, Scalzo et al. 2014). These results suggest that unintended weight loss in PD is cause by abnormal leptin levels. Also adiponectin levels did not show abnormalities and

were similar to age, gender and fat mass matched control (Cassani, Cancello et al. 2011, Rocha, Scalzo et al. 2014); they were associated with weight loss but not BMI in PD patients (abstract in supplement- Tsuboi et al, Parkinson Relat Disord 2007;13:S49- Weight loss and adiponectin levels in patients with Parkinson's disease). Diurnal rhythmicity of all leptin, adiponectin and resistin was not either altered in PD (Aziz, Pijl et al. 2011).

When a person loses weight their ghrelin levels increase, therefore rather unexpected was finding of low ghrelin levels in PD patients with weight loss (Fiszer, Michalowska et al. 2010). Paradoxically, the lower BMI was, the lower plasma active ghrelin concentration was found (Fiszer, Michalowska et al. 2010). The dynamic recuperation from postprandial fall in ghrelin is also disturbed in PD with REM sleep behaviour Disorder (RBD), which suggest alteration in stimulus induced ghrelin secretion (Unger, Moller et al. 2011), implications of such finding on weight loss in PD remain unclear.

Controversial results were published regarding basal ACTH and cortisol levels in PD patients. Both lower (Bellomo, Santambrogio et al. 1991) and higher (Hartmann, Veldhuis et al. 1997, Charlett, Dobbs et al. 1998) plasma and saliva (Djamshidian, O'Sullivan et al. 2011) concentrations of ACTH and cortisol in treatment naive PD patients were reported. Normal levels both basal and after stimulation were detected by Schaefer (Schaefer, Vogt et al. 2008). Acute levodopa administration significantly attenuated a plasma cortisol level which is hypothesized to be connected to reduced 5-HT levels in the brain stem followed by levodopa administration which subsequently reduce hypothalamic function and via the ACTH axis leads to suppression of peripheral cortisol (Muller, Welnic et al. 2007).

Orexins play key role in generation of hunger, and it has been found that orexin/hypocretin system is damaged in PD (Fronczek, Overeem et al. 2007, Thannickal, Lai et al. 2008) . There is an orexin neurons selective loss in PD which correlates with the clinical stage and severity of the disease (Drouot, Moutereau et al. 2003, Thannickal, Lai et al. 2007, Thannickal, Lai et al. 2008, Drouot, Moutereau et al. 2011).

The reports on biochemical and hematological parameters in PD are conflicting and do not provide further insight in the pathogenesis of weight changes. Albumin, calcium, serum alkaline phosphatase, total protein, urea, electrolytes , glucose, hemoglobin, MCV, total peripheral lymphocyte count and B12 in fasting blood samples are within limits in PD patients and only significantly lower peripheral count and serum B12 (Davies, King et al. 1994) was reported, contrary to that significantly lower values of albumin values were found by other authors (Abbott, Cox et al. 1992). Single work reports glucose intolerance in PD patients, which is closely related to adiposity (Lipman, Boykin et al. 1974).

1.6. Weight changes after STN DBS

1.6.1. Antropometric parameters

Apart from therapeutic effects of STN DBS on PD symptoms, motor as well as non-motor side effects have been observed, among which weight gain is prominent. Weight change occurs in STN DBS patient in 50-100% of patients (Romito, Scerrati et al. 2002, Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Guimaraes, Matos et al. 2009, Moro, Lozano et al. 2010, Foubert-Samier, Maurice et al. 2012, Strowd, Herco et al. 2016), however some patients also lose weight after STN DBS (Tuite, Maxwell et al. 2005, Bannier, Montaurier et al. 2009, Novakova, Haluzik et al. 2011). The weight losers had been reported to have

higher BMI on the day of surgery than weigh gainers (Tuite, Maxwell et al. 2005). We described significant weight change observed already within the first months after the surgery before the stimulation start (Novakova, Haluzik et al. 2011), however this has not been supported by others (Tuite, Maxwell et al. 2005). Substantial weight gain with high inter-individual variability is observed within the first 3 months after the procedure (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003, Krack, Batir et al. 2003, Perlemoine, Macia et al. 2005, Montaurier, Morio et al. 2007). From published literature the weight gain 3 months post-surgery is around 3 kg, at 6 months around 4 kg, and 1 year post STN DBS implantation it is + 7kg. Table 1 summarizes weight changes after STN DBS in published literature.

Author, year	# of patients	Result	Amount						
			1 Mth	3 Mth	6 Mth	12 Mth	2 Yrs	5 Yrs	10 Yrs
Macia, 2004	33	weight gain and almost 50% weight loss	NA	NA	NA	**9.7±7**	NA	NA	NA
Barichella, 2003	30	100% weight gain	NA	NA	NA	**9.3±6.2**	NA	NA	NA
Montaurier, 2007	24	weight gain		**3.4±0.6 men 2.6±0.8 women**			NA	NA	NA
Novakova, 2011	27	89% weight gain 11% weight loss	**1.1±2**	NA	NA	**5.2±5.8**	NA	NA	NA
Tuite, 2006	27	weight gain	NS		**4,5**	**9,4**	NA	NA	NA
Romito, 2002	22	100% weight gain	NA	NA	NA	**8,1**	NA	NA	NA
Novakova, 2007	23	weight gain	NA	NA	NA	**9,4**	NA	NA	NA
Perlemoine, 2005	32	weight gain	NA	NA	NA	**9.7±7.1**	NA	NA	NA
Sauleau, 2009	32	weight gain	NA	NA	**5.7±5.4**		NA	NA	NA
Jorgensen, 2012	10	weight gain	NA	NA	NA	**4,7**	NA	NA	NA
Strow, 2010	88	weight gain	NA	NA	NA	**2,5**	NA	NA	NA
Foubert-Samier, 2012	47	78.7% weight gain 14.9 % weight loss	NA	NA	NA	NA	NA	**7.2±8.1**	NA
Castrioto, 2011	18	weight gain	NA	NA	NA	**17.1**	NA	**6.9**	**1.3**
Bannier, 2009	22	weight gain	NA	**3.1**	NA	NA	NA	NA	NA
Strand, 2016	35	weight gain	NA	NA	NA	NA	**1.3**	NA	NA

Table 1. Summary of weight changes in PD patients post DBS

Observations what happens with weight in a long term are inconsistent, but it seems that the body weight tends to stabilize (Novakova, Ruzicka et al. 2007, Rodriguez-Oroz, Moro et al. 2012), however weight loss as well as further weight gain were also described (Novakova, Ruzicka et al. 2007, Locke, Wu et al. 2011, Foubert-Samier, Maurice et al. 2012). The observation showed, that the weight increase beyond the first 2 years after surgery is not linear (Foubert-Samier, Maurice et al. 2012), the only ten year follow up study found a trend toward a loss of weight (Castrioto, Lozano et al. 2011). Gender prevalent weight gain

remains conflicting, we are the only group that reported women gaining significantly more weight post-surgery than men (Novakova, Haluzik et al. 2011); but most did not find significant difference between the genders (Macia, Perlemoine et al. 2004, Foubert-Samier, Maurice et al. 2012, Strowd, Herco et al. 2016), although there was a trend toward male weight gain preponderance. BMI changes paralleled weigh changes most of the time.

Percentage of fat mass increases after STN DBS (Macia, Perlemoine et al. 2004), however significant inter- individual variations and gender related difference in the quality of body weight gain were reported; in men 2/3 of body weight gain was due to an increase in FFM while women gained only fat (Montaurier, Morio et al. 2007).

As one would expect, weight changes have been shown to correlate with improved UPDRS "on" and " off" motor scores (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003), however surprisingly weight gain often does not correlate with UPDRS motor scores, dyskinesia duration and disability changes, or the HY stage (Sauleau, Leray et al. 2009, Locke, Wu et al. 2011). Additional study reported that younger age was associated with weight gain (Strowd, Herco et al. 2016).

Weight gain seems to be independent of target and procedure; it has been observed in STN DBS (Barichella, Marczewska et al. 2003, Krack, Batir et al. 2003, Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007, Bannier, Montaurier et al. 2009, Novakova, Haluzik et al. 2011, Foubert-Samier, Maurice et al. 2012, Ruzicka, Novakova et al. 2012), GPi-DBS (Strowd, Cartwright et al. 2010, Locke, Wu et al. 2011) and as well in pallidotomy (Dalvi, Winfield et al. 1999, Ondo, Ben-Aire et al. 2000, Gironell, Pascual-Sedano et al. 2002). Publications comparing GPi and STN weigh gain showed that the weight gain associated with STN is more pronounced (Barichella, Marczewska et al. 2003, Sauleau, Leray et al. 2009, Mills, Scherzer et al. 2012). Interestingly a long term follow up study comparing post- operative weight changes after GPi and STN

revealed that starting after 6 months post-surgery the opposite weight changes among targets occur, where gradual average weight gain for the STN group was observed contrasting with a subsequent gradual weight loss in the GPi group at 3 years follow up (Abstract, MDS Congress 2017, Shah S et al: Weight changes in STN and GPi Deep brain stimulation: Long term follow up).

1.6.2. The mechanism of weight changes after STN DBS

The mechanism of weight gain following STN DBS has not been yet fully elucidated. In any case, weight gain is achieved by a positive energy balance for which several mechanisms might play a role.

Significant decrease in energy expenditure was reported after STN DBS (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Jorgensen, Werdelin et al. 2012). The decrease in total energy expenditure after surgery was 13% which theoretically would lead to a weight gain at about 20 kg after 1 year assuming unchanged daily caloric intake postoperatively, and all the extra energy deposited as fat (Jorgensen, Werdelin et al. 2012). The decrease in EE may be explained by multiple factors. The simplest explanation would be reduction of LID, however correlation between weight gain and dyskinesia reduction has not always been found (Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007). Improvement in motor symptoms, markedly reduction of rigidity and tremor contribute to decrease in EE and subsequently to weight gain; correlations between reduction in UPDRS III and weigh gain have been confirmed (Barichella, Marczewska et al. 2003, Foubert-Samier, Maurice et al. 2012), some however did not confirm this finding (Walker, Lyerly et al. 2009, Novakova, Haluzik et al. 2011) Changes in leisure time activities may also contribute to changes in energy expenditure, however these were not reported (Jorgensen, Werdelin et al. 2012). Information regarding dietary intake change

after STN DBS varies among literature and often bear limited reproducibility; Barichella reporting no difference in food intake and Danish group reduction (Jorgensen, Werdelin et al. 2012). Finally, a reduction of levodopa – induced behavioral hyperactivity post DBS may contribute to decrease in EE and subsidize weight gain (Lhommee, Klinger et al. 2012, Kistner, Lhommee et al. 2014); however correlation between changes in LEED change and weigh change was not confirmed in many reports (Barichella, Marczewska et al. 2003, Montaurier, Morio et al. 2007, Sauleau, Leray et al. 2009, Walker, Lyerly et al. 2009, Novakova, Haluzik et al. 2011, Foubert-Samier, Maurice et al. 2012, Mills, Scherzer et al. 2012).

Given the structural and functional complexity of the subthalamic area, it is conceivable that the stimulating DBS electrode influences body weight, especially if it is placed close to the structures involved in the regulation of energy expenditure, food intake or reward, such as the lateral hypothalamic area (Berthoud and Morrison 2008), medical forebrain bundle (Wise 2005) or the limbic part of the STN (Ruzicka, Jech et al. 2012). Ruzicka et al found that weight gain is associated with medical contact site of subthalamic stimulation and is inversely related to the distance of the contacts from the wall of the third ventricle (Ruzicka, Jech et al. 2012). Kistner points up in his review that this finding does not help us to distinguish between current diffusion to the hypothalamus or to the mesolimbic part of the STN (Kistner, Lhommee et al. 2014). Based on the report where lesion of the STN without lesioning the hypothalamus in rats leads to impulsive feeding behavior (Baunez, Amalric et al. 2002), Kistner argued that weight gain is related to lesioning effect of the mesolimbic STN (Kistner, Lhommee et al. 2014). Serranova and colleagues found increased sensitivity to food reward cues which correlated with postoperative weigh gain (Serranova, Jech et al. 2011, Serranova, Sieger et al. 2013).

STN DBS may influence neural regulation of gastric emptying; one study demonstrated improvement of gastric function after STN DBS (Arai, Arai et al. 2012) which can alleviate upper gastrointestinal symptoms such as heavy feeling in the stomach, bloating, nausea or feeling sick and belching (Arai, Arai et al. 2012) and which subsequently can facilitate food intake. However our patients did not report any change in nausea after STN DBS (Novakova, Ruzicka et al. 2007).

As discussed in the chapter above, neuroendocrine dysregulation may play a role in weight gain after STN DBS.

Finally the patients might be just normalizing their weight after previous weight loss, however weight gain often exceeds previous weigh loss (Tuite, Maxwell et al. 2005, Novakova, Ruzicka et al. 2007, Foubert-Samier, Maurice et al. 2012).

1.6.3. Food related parameters in STN DBS

The data on food related parameters in STN DBS PD patients are sparse and rather conflicting. The failure to show consistent correlations between parkinsonian motor symptoms and energy metabolism led to suggestion that neuroendocrine dysregulation is present post STN DBS which induces temporary hypothalamic dysregulation causing the weight gain (Corcuff, Krim et al. 2006, Escamilla-Sevilla, Perez-Navarro et al. 2011, Novakova, Haluzik et al. 2011, Markaki, Ellul et al. 2012, Ruzicka, Novakova et al. 2012). The main focus laid on orexigenic factors such as ghrelin and NPY; and fat tissue hormone leptin.

Markari et al found increased ghrelin levels 6 months after the surgery. Observed weight gain significantly correlated with increased ghrelin levels at month 3 and 6. On contrary, Corcuff found no acute changes in ghrelin levels investigating patients with or without ongoing STN stimulation, but when L dopa was administered to stimulated patient, there was a marked reduction in

ghrelin levels (Corcuff, Krim et al. 2006). L dopa reduction post STN DBS is common; therefore the L dopa reducing effect on ghrelin is mitigated and ghrelin can exert its appetite stimulating effect and thus weight gain. These results are in line with increased ghrelin levels reported (Markaki, Ellul et al. 2012).

NPY circulating levels increased significantly 3 months following the procedure (Escamilla-Sevilla, Perez-Navarro et al. 2011, Markaki, Ellul et al. 2012) together with leptin (Escamilla-Sevilla, Perez-Navarro et al. 2011), which raised hypothesis that DBS interferes with the inhibitory action of leptin where physiologically reciprocal inhibition between leptin and NPY exists. The NPY results should be however interpreted with caution since these are measured peripherally but NPY is centrally produced peptide and the peripheral concentration likely does not reflect exact central levels. Despite the weight gain of our patients we found no significant change in leptin levels up to 12 moths post implantation (Novakova, Haluzik et al. 2011), this is in line with Markaki's work, where as well no significant change in leptin was found. (Markaki, Ellul et al. 2012).

The anatomical proximity and functional connections of the STN and hypothalamic – pituitary axis (HPA) led to investigation of HPA hormones.

Two teams observed decreased cortisol levels following STN DBS (Novakova, Haluzik et al. 2011, Markaki, Ellul et al. 2012, Ruzicka, Novakova et al. 2012) which started at 2 months after the surgery still remaining significantly reduced at 12 months after DBS implantation (Novakova, Haluzik et al. 2011). On contrary Seifried revealed no change in basal HPA hormones and intact diurnal rhythmicity (Seifried, Boehncke et al. 2013) with the exception of lower 24-hour cortisol levels with a pronounced reduction in the evening hours leading to cortisol levels within the range of normal volunteers. This result correlated with improved postoperative depression and likely reflected postoperative adaptation with stress reduction presumably due to improved mobility and quality of life (Seifried, Boehncke et al. 2013). Ruzicka with colleagues further investigated relationship between contact location, cortisol and weight gain,

and found that the level of cortisol decreased greater in patients with more medial location of active contact than in those with one or both active contacts more laterally (Ruzicka, Jech et al. 2015). Besides the above listed cortisol, leptin and ghrelin, we evaluated other food related parameters such as total protein, albumin, prealbumin, cholesterol, triglycerides, insulin, glycemia, glycated hemoglobin and insulin like growth factor 1 (IGF1), thyreotropin stimulation hormone (TSH), adiponectin and resistin before surgery, at 2, 4, 6 and 12 months after DBS implantation. Besides cortisol we found no significant change in any of the measured parameters (Novakova, Haluzik et al. 2011, Ruzicka, Novakova et al. 2012). On contrary from our results, Markaki found significantly increased albumin and total protein at months 3 and 6, and total protein elevation 3 months post-surgery (Markaki, Ellul et al. 2012).

2. AIMS OF THE STUDY

Study 1. Frequent weight gain has been found as a non-motor symptom across multiple studies evaluating post-operative changes in patients with PD STN DBS. In agreement with published studies we have as well noticed increasing weight in our patients. The first study aimed to confirm weight changes in group of advanced PD patients treated with STN DBS in our center.

Study 2. As we previously confirmed body weight changes in PD STN DBS by retrospective evaluation we needed to reciprocate these findings by prospectively evaluating weight evolution and related anthropometric parameters after STN DBS. The second aim of Study 2 was to explore whether the weight gain in STN DBS treated patients was associated with changes in hormones involved in the regulation of energy homeostasis and food intake.

Study 3. Based on the anatomical and functional complexity of STN we aimed to explore whether weight changes and motor improvement seen after STN DBS are dependent on active contact position within the STN.

3. Hypothesis

Study 1. We hypothesized that patient treated with STN DBS in our center gain weight in correspondence with published sources.

Study 2. We hypothesized that we will be able to confirm evolution of weight changes following STN DBS PD treated subjects and that these will be accompanied by abnormalities in hormones involved in the regulation of food intake and energy homeostasis.

Study 3. We hypothesized that weight gain may be associated with medial contact position in the STN.

4. Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease

4.1. Material and Methods

All 25 patients who received STN DBS between years 2000 and 2003 in the Movement disorders Center, Charles University, Prague, were included in the study. They were 16 men and 9 women, mean age in the time of intervention was 55 years (range 42-65), and mean PD duration 14 years (range 9-21).

Repeated retrospective survey was used as a method. The mean interval between DBS implantation and the first survey was 19 months (range 1-45). The subjects were provided with a structured questionnaire (44 questions) regarding their family and personal history focusing on potential presence of metabolic syndrome. Further specific questions concerned body weight changes in the period preceding PD, and in the course of PD, before and after the implantation of DBS. All addressed participants returned the questionnaire.

Body mass index (BMI) was calculated from a person's weight in kilograms divided by height in meters squared (BMI=kg/m2). Accordingly, patients were divided into 6 groups: underweight (BMI under 18.5), normal weight (BMI from 18.5 to 25), overweight (BMI 25-30), 1st degree obesity (BMI 30-35), 2nd degree obesity (BMI 35-40) and 3rd degree obesity (BMI over 40).

We repeated the survey with the same group twelve months later focusing on body weight and metabolic syndrome signs.

All patients were neurologically evaluated using Unified Parkinson Disease Rating Scale (UPDRS) and MDS scale of dyskinesias within one week before and approximately 1 year after DBS implantation. Daily doses of dopaminergic medication were converted to Levodopa Equivalent Daily Dose, LEDD (100 mg

of standard levodopa equals 150mg of CR levodopa, 1 mg pergolide or pramipexole, 10 mg bromocriptine, or 6mg ropinirole).

Body weight values before and after DBS were compared using paired Student's t-tests. Correlations between clinical parameters and body weight changes were calculated using Spearman's rho coefficient.

4.2. Results

Within one year from DBS implantation, 23 out of 25 patients did experience motor improvement including alleviation of motor fluctuations and dyskinesia. Two patients were excluded from the study of body weight changes. One because pf discrepancies between the data provided in the patient's questionnaire, our observation, and the data provided by family members. The other one has had DBS interrupted in the time of the first survey as the stimulator was temporarily withdrawn due to inflammatory complications.

Body weight changes

All 23 patients reported body weight gain after DBS implantation (Table 2, Figure 6). In the first survey, we found overall mean increase in weight of 9.4 kg (range 1-25 kg), i.e. +13%, $p<0.0001$. In women, there was an average increase in weight of 12.8 kg (range 6-25kg), i.e. +21%, $p<0.01$, and in men, weight increased by 7.6 kg (range 1-20 kg), i.e. +10%, $p<0.0001$. Comparing mean weight increases in men and women, there was a trend towards difference in genders ($p=0.07$). In the second survey, 14 subjects lost weight, 3 remained stable, and 6 reported further weight gain compared to the first survey. The mean weight change compared to the first survey was -1.4kg (range -6 to +11 kg) i.e. –2%, $p=0.11$;-2.4kg in men (range -6 to+4kg) i.e.-3%, $p<0.01$ and +0.5kg in women (range -6 to +11kg) i.e. +1%,$p=0.79$. Comparing the second survey to the values before DBS, there was a mean change of +13 kg (from -4 to +33kg) comparing to the lowest weight before PD onset and a mean change of +4kg

(from -9 to 25kg) comparing to the highest weight the patients ever had before PD onset. In this last comparison, body weight increased in 13, decreased in nine, and two patients were unable to state their highest weight before PD.

	Before DBS		**After DBS: 1st survey**			**After DBS: 2nd survey**		
	Mean weight (kg)	Range (kg)	Mean weight (kg)	Range (kg)	Mean weight change (1^{st} survey – before DBS) (kg)	Mean weight (kg)	Range (kg)	Mean weight change (2^{nd} survey – 1^{st} survey) (kg)
All	71.0	50-96	80.4	58-105	9.4 ***	79.0	60-100	–1.4
Men	75.9	60-96	83.5	70-105	7.6 ***	81.1	66-100	–2.4
Women	61.9	50-79	74.6	58-90	12.8 *	75.1	60-90	+0.5

Table 2. Weight changes after DBS (Novakova, Ruzicka et al. 2007)

***** p<0.0001, * p=0.01**

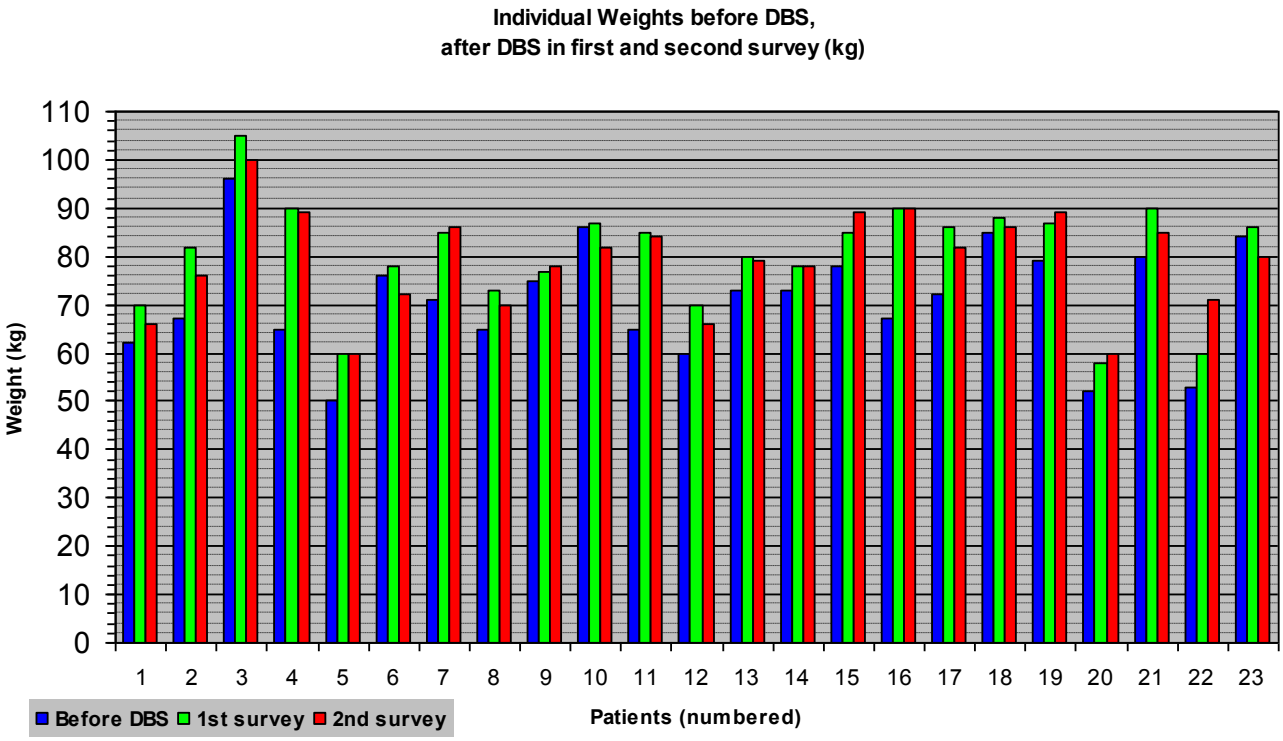


Figure 6. Overview of the individual weights of the patients (Novakova, Ruzicka et al. 2007)

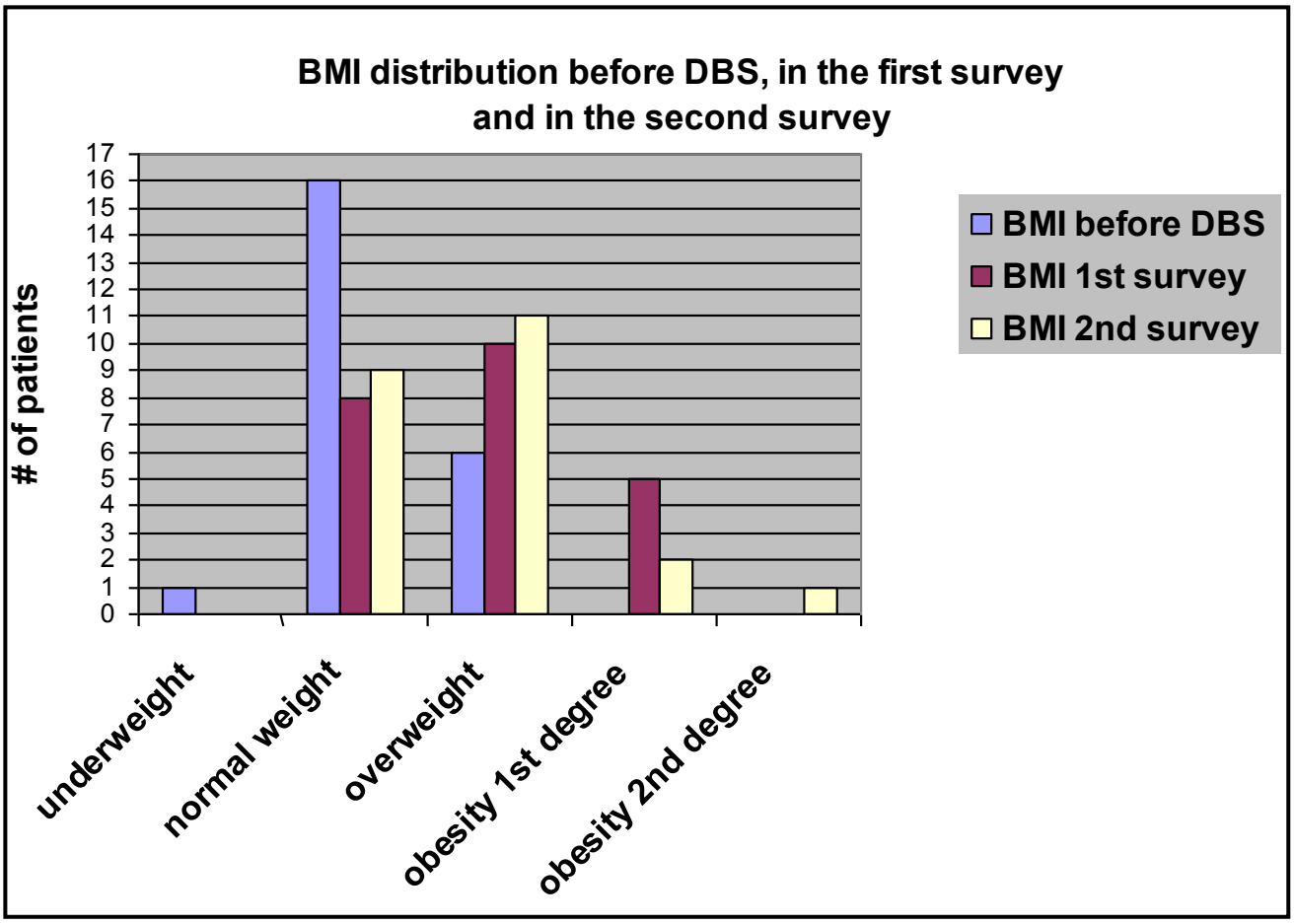


Figure 7. BMI distribution before DBS, in the first and second survey (Novakova, Ruzicka et al. 2007) *BMI – body mass index

No significant correlation was found between changes in UPDRS and MDS scores of dyskinesia and weight changes. Nor did we find any significant correlation between weight changes and the changes in LEDD.

After DBS, all patients increased their BMI. The mean BMI before STN DBS was 23.7 (standard deviation 2.9). In the first survey, it increased to 27.0 kg/m2 (±3.6) and in the second survey, it remained nearly unchanged at 26.6 ((±3.5)kg/m. Shifts in BMI categories occurred, too. Comparing to BMI values before DBS, in the first survey two patients increased by two BMI categories, 11 patients shifted by one BMI category (one patient increased from underweight to normal weight, 7 increased from normal weight to overweight, and 3

increased from overweight to the 1st degree of obesity. In the second survey, 17 patients did not demonstrate any further changes in their BMI category, 2 patients shifted down 1 category (from 1st degree of obesity to overweight), and 1 patient shifted up one category from the 1st degree of obesity to the 2degree of obesity (figure 7).

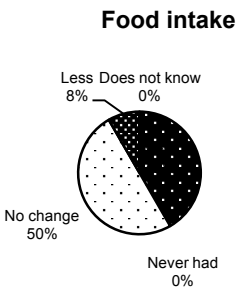
Unpublished results

Body feelings and habits, nausea

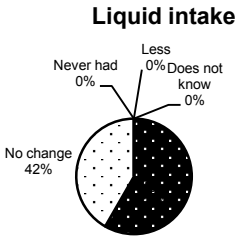
12 out of 23 patients (52%) claimed increased appetite which subsequently lead to increased food intake in 42% of patients (Figure 8-graph #3). Majority of patients have also increased liquid intake (Figure 8 -graph #4). The distribution of answers in the last two graphs of Figure 8 referring to perspiration and feelings of cold (graph # 5 and 6) is je even, nevertheless 2/3 of patients noted change in the habits. Changes in these last two categories may point towards direct influence of DBS on hypothalamus. None of the patients reported nausea or vomiting prior or post procedure. 39% claimed that they perform less sports in comparison with a period of 1 year before DBS implantation and only 17% declared doing sports more frequently. 3 patients from the cohort stopped smoking post DBS.

In addition (not shown in chart) 39% of patients perform sports less frequently than 1 year before DBS.

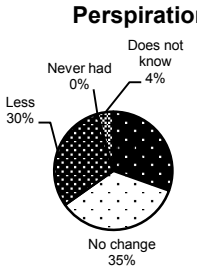
Graph 3



Graph 4



Graph 5



Graph 6

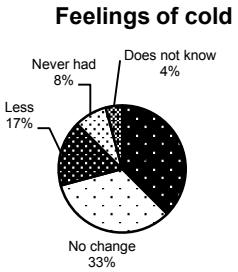


Figure 8. Body feelings and habits, nausea (own data, unpublished).

4.3. Discussion

In this retrospective study, we found weight gain accompanying motor improvement in all 23 patients evaluated after STN DBS. Therefore, we confirm previous findings of weight increase after STN DBS. Similarly to other reports (Barichella, Marczewska et al. 2003, Krack, Batir et al. 2003, Macia, Perlemoine et al. 2004, Tuite, Maxwell et al. 2005), average weight gain was nearly 10 kg. Surprisingly, women in our study tended to gain more weight than men, while in none of the previous reports such difference between genders was found. Weight gain in our patients did not correlate with any of the clinical variables reflecting motor improvement neither with reduction of dopaminergic treatment following STN DBS.

We have to admit that due to the method used (retrospective questionnaire) and different intervals for each patient between the implantation and the time of the first survey, our results are not completely comparable with previous reports. However, in our study, we observed patients for a longer period of time and repeated the same survey on the study group one year later. Thanks to this, beside weight gain following DBS we found out that at longer intervals, it is possible to observe weight loss reversing the previous weight increase but rarely back to the same level as before DBS. It was unclear how long after the DBS implantation the trend change from increasing to decreasing weight occurred. Possibly, some patient could have already been in a decreasing weight trend when we surveyed them first time, however, they could still report an increase in weight compared to the time before DBS. The weight change interval seems to be very individual. In fact, within 12 months following the first survey, weight increased in three patients with the longest interval as well as in the three patients with the shortest interval from the implantation.

In brief, despite different observation methods, the findings from several centers agree in demonstrating weight gain in patients with PD after STN DBS. The mechanism of this weight gain is still unclear and various hypothetical explanations can be suggested.

Firstly, weight gain following STN DBS might reflect a reversal of previous weight loss in PD. Indeed, weight loss has been observed since the early stages of PD and it usually progresses during its course (Marcus HS 1992, Marcus HS 1993, Davies, King et al. 1994, Beyer, Palarino et al. 1995).

According to one study, weight loss in PD patients may begin 2-4 years before the diagnosis is made (Chen, Zhang et al. 2003). One reason for weight loss starting from the beginning of PD may be worsened exploitation of energy from

food due to gastroinstestinal visceromotor impairment. Accordingly, recent pathologic findings showed involvements of bulbus olfactorius and visceromotor nuclei of the brainstem since the earliest stages of the disease (Braak, Ghebremedhin et al. 2004). Also, olfactory dysfunction and motor disability can lead to a decrease of appetite and, in consequence, to a decrease of energetic input (Abbott, Cox et al. 1992, Beyer, Palarino et al. 1995). However, several studies have reported equal or even higher intake of energy in PD patients compared to healthy subjects (Davies, King et al. 1994, Toth, Fishman et al. 1997, Chen, Zhang et al. 2003). Surprisingly, according to these studies, energetic input starts to increase when weight begins to decline (Beyer, Palarino et al. 1995). The fact that weight loss occurs despite higher intake of energy could mean that it is caused by higher energetic output. This explanation was supported by a couple of studies, which proved than an increase of energetic output was related to severe muscle rigidity (Levi, Cox et al. 1990, Marcus HS 1992) or dyskinesias, where BMI was negatively correlated with severity of dyskinesias (Ondo, Ben-Aire et al. 2000). It was also found that weight loss correlates with the disease severity (Beyer, Palarino et al. 1995), the degree of hypokinesia (Palhagen, Lorefalt et al. 2005) or with cognitive decline (Lorefalt, Ganowiak et al. 2004). Consequently, weight gain can be explained by motor improvement following DBS, especially owing to a reduction in exhausting dyskinesias. Subsequently, the energy output may be reduced, as it was demonstrated in one previous study (Macia, Perlemoine et al. 2004). Nevertheless, in agreement with our results, the study did not find and correlation between weight gain and the reduction of dyskinesias according to detailed dyskinesia scales (Macia, Perlemoine et al. 2004). Another study that demonstrated a correlation between weight change and severity of dyskinesia,

did so only according to raw UPDRS IV scores that are based on subjective patient evaluation (Barichella, Marczewska et al. 2003).

Secondly, weight gain can be related to changes in medication, especially with regard to a reduction or withdrawal of dopaminergic drugs can cause gastrointestinal discomfort, nausea and vomiting. Therefore, a reduction of dopaminergic drugs might lead to improved alimentation due to an alleviation of the side effects. Nevertheless, neither in our group nor in a previous report (Barichella, Marczewska et al. 2003) patients complained of nausea and vomiting before or after STN DBS. There remains a possibility that dopaminergic therapy can directly influence metabolism and energy consumption. In fact, only a few studies investigated levodopa therapy in relation to weight in PD patients (Muller, Woitalla et al. 2000, Palhagen, Lorefalt et al. 2005). Palhagen et al. found that patients with an early stage of PD were losing weight even before the initiation of dopaminergic treatment and the loss of weight processed after levodopa was given (Palhagen, Lorefalt et al. 2005). No correlation was found between levodopa dose and weight loss. It was hypothesized that motor improvement induced by levodopa led to changes in energetic input/output ratio. Possible lipolytic or other metabolic effects were suggested as well (Vardi, Oberman et al. 1976). However, our data do not support this assumption. In accordance to a previous work (Barichella, Marczewska et al. 2003), weight gain did not correlate with LEDD reduction in our patients. In another study, despite a correlation found between LEDD reduction and weight gain, the decreases of LEDD did not correlate with changes in energy expenditure (Macia, Perlemoine et al. 2004).

Finally, weight changes could reflect a direct influence of DBS on autonomous functions and metabolic regulation. The question then would be whether STN DBS specifically normalizes metabolic disturbances induced by PD or it is rather

a general effect of stimulation. Despite all the above-mentioned observations, it does not seem that the weight increases following STN DBS in patients with PD reflect just an indirect effect of stimulation rather than just a reversal of pathologic weight loss. In this context, the closed anatomic relationship between the subthalamic nucleus and lateral hypothalamus should be taken into account. Hypothalamic pathways and connections of “chemical systems” traverse the medial forebrain bundle in close vicinity to STN, together with STN connections to the brainstem. Consequently, STN DBS has a chance to influence these pathways as well as adjacent neurons in the lateral hypothalamic area that are involved in feed habits and energy expenditure regulation (Cerri and Morrison 2005). In conclusion, STN DBS in PD patients is frequently accompanied by body weight gain. The mechanisms that cause the weight gain are not fully understood. The decrease in energetic output appears as a major contributing factor and may reflect a direct influence of STN DBS on brain systems regulation metabolism and food intake.

5. Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation

5.1. Materials and methods

Twenty-seven patients that received STN DBS were enrolled in the study (21 men, 6 women; age at time of intervention: mean 56.8±(SD)7 years. Range 42-68; disease duration: mean 12.5±4 years, range 7-23. All subjects suffered from severe motor fluctuations that were not improved by adjustments in antiparkinsonian medication. The study was approved by the local Ethics Committee, and all participants provided signed, informed consent prior to enrollment.

Stimulation was initiated four weeks after implantation of the electrodes. DBS setting and medication were subsequently adapted to achieve the best possible compensation. Each subject was evaluated on the day of the interview (baseline, pre-surgery) after at least 12 hours of discontinuing all antiparkinsonian drugs (MED-OFF), then at one month, before the setting-up (MED-OFF/DBS-OFF), after the initiation of stimulation (MED-OFF/DBS-ON). Further assessments were completed at 2, 4, 6 and 12 months after surgery. The sum of total electrical energy delivered by DBS in 12 months was calculated using the formula proposed by Koss et al (Koss et all. 2005).

Motor status was evaluated using the Unified Parkinson Disease Rating Scale motor subscale (UPDRS III). Eating related questionnaires (food intake, hunger, appetite) were administered at each visit. Anthropometric examination included body weight and height, body mass index (BMI=weight in kg/height in m2), and waist circumference. At each visit, 5 ml of blood was withdrawn between 7-8 AM following an overnight fast, and serum biochemical parameters (total protein, albumin, prealbumin, cholesterol. Triglycerides, insulin, glycemia,

glycated hemoglobin and insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), cortisol, leptin, adiponectin, resistin and ghrelin were assessed by standard laboratory methods using commercial kits: Serum insulin concentrations were measured by RIA kits (Cis Bio International, Gif-sur-Yvette, France). Sensitivity was 2.0 µIU/ml, and the intra- and inter-assay variability was 4.2 and 8.8%, respectively. IGF-1: IRMA kit (Immunotech, Prague, Czech Republic), 2ng/ml, 6.3 and 6.8%. Leptin: ELISA kit (BioVendor, Brno, Czech Republic), 0.12 ng/ml, 1.7 and 8%. Adiponectin: RIA kit (Linco Research, St. Charles, MO), 1.0 ng/ml, 1.8 and 9.3%. resistin: ELISA kit (BioVendor, Brno, Czech republic), 0.2 ng/ml, 3.1 and 6.5%. Ghrelin: RIA kit (Linko Research, Saint Charles, MO), 93 pg/ml, 10 and 14.7%, respectively. The other biochemical parameters were measured by standard laboratory methods using commercial kits.

Daily doses of dopaminergic medication at baseline, 1 month, and 12 months following the surgery were converted to Levodopa Equivalent Daily Dose (LEDD; 100 mg of standard levodopa equals 150mg of CR levodopa, 1mg pramipexole, or 6mg ropinirole).

Statistical analyses were performed using Statigraphics software (Warrenton, VA). Non –parametric tests were used as a substantial portion of the data did not fit a normal distribution (Mann-Whitney test, Kruskal-Wallis test, paired signed-rank test, Spearman's rank correlation). Wherever appropriate, results were corrected for multiple comparisons by Bonferroni correction.

5.2 Results

Motor and Pharmacological Outcomes

Comparison of the MED-OFF state at baseline to the MED-OFF/DBS-OFF condition at one month after surgery did not reveal any significant change, with mean UPDRS III scores of 33.0± (SD)11 and 34.7±10,respectively ($p<0.8$). In the MED-OFF/DBS-ON condition at one month after surgery, the mean UPDRS III score significantly decreased to 17.2±6 ($p<0.001$). The MED-OFF/DBS-ON UPDRS III score at 12 months did not significantly change (14.5±7, $p<0.14$) in comparison to one month after surgery.

The LEDD significantly decreased from 1330±538mg at baseline to 1196±401 mg ($p<0.001$) at one month, and to 704±429 mg ($p<0.001$) at 12 months after surgery.

DBS Parameters

The average sum of stimulation energy delivered over the 12 month study period was 3412±1280 J. No correlation between change in body weight and the energy of stimulation was found (12 month vs baseline, $rs = 0.1844$, $p<0.3$).

Anthropometric Parameters

On average, we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period (Table 3). Notably, a significant change in body weight was observed already at one month following surgery, i.e., before stimulation was started, in comparison to baseline: +1.1±2 kg, range –2.6 to 5.0, ($p<0.05$). Change in mean weight from baseline to 12 months following STN DBS implantation was +5.18±5.8 kg, range –6.30 to +19.80, ($p<0.001$) (Figure 9). At month one, taken individually, 17 patients gained weight compared to baseline while weight loss was noted in 10 patients. At month

twelve, 24 patients gained weight and 3 patients had lower weight compared to baseline. In examining gender differences, body weight increased at 12 months after STN DBS implantation by 9.0±5 kg in women (range 5.0 to 18.3) and 4.1±6 kg in men (range –6.3 to 19.8).

Body weight and BMI differed significantly between the genders, with a greater increase in women ($p<0.05$, $p<0.01$, respectively). A borderline correlation between weight gain following STN DBS and PD duration was observed ($rs = 0.418$, $p<0.05$), but not with age at PD onset. No significant correlation was found between the change in LEDD and change in weight. Most of the subjects did not report any changes in food intake, hunger or appetite.

Laboratory Parameters

A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months ($p<0.01$, corrected), with no significant changes in other tested hormones or biochemical parameters (Table 3, Figure 9). A positive correlation between leptin levels and body weight ($rs = 0.299$, $p<0.001$) and body fat percentage ($rs =0.343$, $p<0.05$) was found. Body weight negatively correlated with adiponectin ($rs = –0.604$, $p<0.001$), positively with ghrelin ($rs = 0.253$, $p<0.01$) and did not significantly correlate with cortisol ($rs = –0.114$, $p<0.2$).

Hormonal and Antropometry parameters	Pre surgery DBS	1 month after DBS		12 months after DBS	
	mean □ SD	**mean □ SD**	***p uncorr***	**mean□ SD**	***p uncorr.***
Body weight [kg]	78.7±16	79.8±16	0.0185**	83.9±15	0.0001***
BMI [kg/m2]	25.82±4.0	26.11±3.8	0.0251**	27.51±3.7	0.0001***
Waist circumf. [cm]	94.01±13.0	94.95±12.6	0.08	98.76±11.7	0.0010**
Body fat [%]	21.57±7.4	21.94±7.4	0.20	25.82±5.9	0.0030*
Leptin [ng/ml]	7.61±8.68	6.84±6.71	1.00	9.48±8.99	0.09
Adiponectin [ng/ml]	21.25±12.27	23.14±12.49	0.30	19.76±9.55	0.36
Resistin [ng/ml]	7.20±2.99	6.40±2.82	0.08	6.95±2.71	0.74
Ghrelin [ng/l]	1.30±0.66	1.21±0.38	0.78	1.12±0.44	0.34
Insulin [IU/ml]	7.78±4.61	11.51±12.33	0.34	8.02±3.84	0.56
Cortisole [nmol/l]	688.96±149.41	618.78±159.50	0.09	531.3±179.94	0.0008**
IGF 1 [ng/ml]	180.73±76.11	184.50±67.06	0.84	169.75±53.06	0.21
TSH [mIu/l]	2.29±2.26	1.82±1.18	0.43	1.9±1.47	0.97

Table 3: Patients´ anthropometric parameters and selected hormonal levels pre-surgery (baseline), 1 month and 12 months after STN DBS (Novakova, Haluzik et al. 2011)

DBS, deep brain stimulation; BMI, body mass index; pre-surgery = baseline. TSH, thyreotropin stimulating hormone; IGF1, insulin like growth factor 1.
Statistical significance of the difference in hormone levels measured at month twelve, one and at baseline was tested by paired signed-rank test; Bonferroni correction at level p<0.05 (*), p<0.01 (**), p<0.001(***)

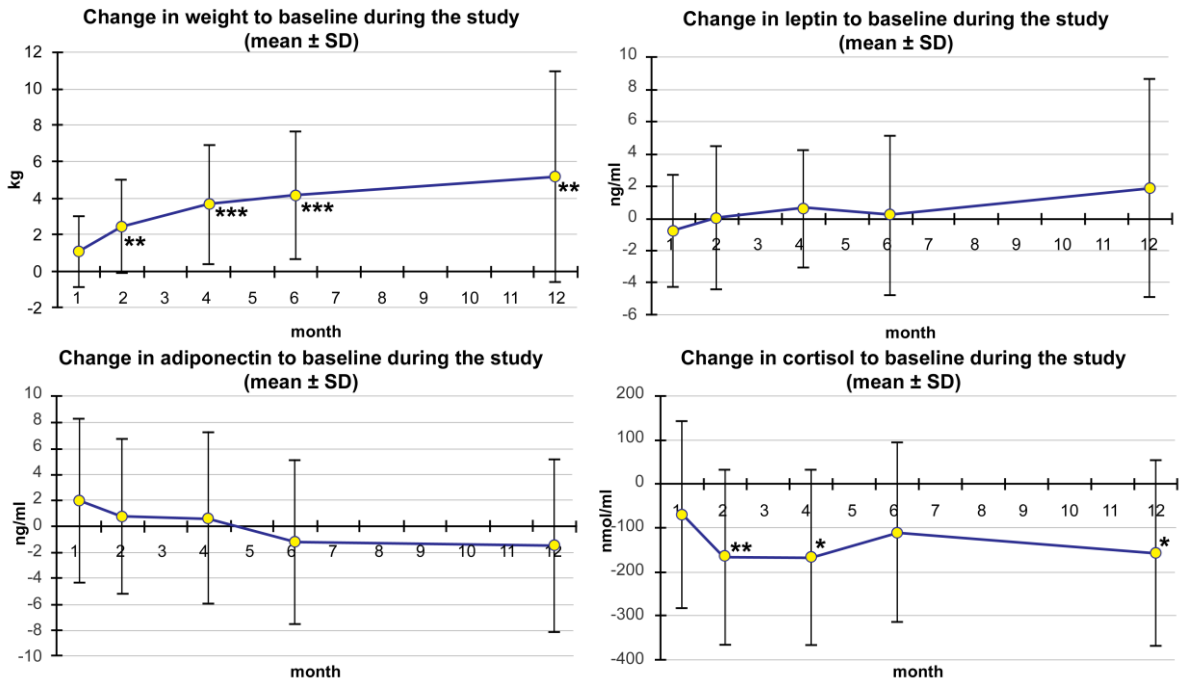


Figure 9: Mean changes in weight, leptin, adiponectin, and cortisole during the study. (Novakova, Haluzik et al. 2011)
X axis: individual measurements on 1, 2, 4, 6, 12 months after the surgery. Y axis: difference from baseline, measured parameter and its units

5.3. DISCUSSION

In this prospective study, we tested the hypothesis that weight changes in PD patients treated with STN DBS are connected with abnormalities in the hormonal regulation of food intake. In concordance with previous studies (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Perlemoine, Macia et al. 2005, Tuite, Maxwell et al. 2005, Montaurier, Morio et al. 2007), body weight increased in most of our patients, together with increasing BMI, waist circumference and body fat percentage within one year on STN DBS. Body weight correlated positively with serum levels of leptin and inversely with adiponectin, which correspond to the physiological regulatory mechanisms of food related processes (Meier and Gressner 2004). In addition, ghrelin positively correlated with weight in our patients. This corroborates previous findings that were considered paradoxical in PD patients where weight loss usually occurs with the disease progression – the lower BMI was, the lower ghrelin levels were

found (Fiszer, Michalowska et al. 2010). However, in accordance with Corcuff *et al.*, we did not observe any increase in ghrelin following STN DBS (Corcuff, Krim et al. 2006). In fact, since the peripheral ghrelin was measured, the results may not reflect possible changes in centrally released ghrelin that mainly participates in the regulation of food intake and body weight.

As the most prominent hormonal change, serum levels of cortisol were found to significantly decrease on STN DBS, although cortisol should typically increase in the course of truncal fat accumulation and increasing body weight (Reynolds 2010). This finding was also observed in Markaki's study (Markaki, Ellul et al. 2012), where at 3 months after STN DBS, Markaki and colleagues noticed significant decrease in blood cortisol (-23.9%, $p < 0.0002$), in our study cortisol lowered significantly at 2 months and remained significantly reduced compared to baseline at 12 months after DBS implantation. Hence, direct effects of STN stimulation on adjacent nerve fibers and nuclei must be considered. STN DBS may hypothetically act on the hypothalamus by suppressing the secretion of CRF with a subsequent decrease in the production of cortisol. Since the level of corticotropin-releasing factor is low, its catabolic effect is mitigated: therefore, the homeostatic balance shifts towards predominance in anabolic reactions. Indeed, in rats exposed to high-frequency electrical stimulation of the lateral hypothalamus, body weight changes occurred even if no difference was observed in food intake between stimulated and unstimulated animals (Sani, Jobe et al. 2007). Our hypothesis is indirectly supported by previous reports showing that cortisol levels were significantly higher in PD patients compared to healthy controls and that cortisol concentrations significantly decreased after levodopa intake, particularly in patients with more advanced stage of PD (Charlett, Dobbs et al. 1998, Muller, Welnic et al. 2007).

No consistent changes in food-related behavior were recorded in our patients. This is in agreement with previous studies indicating no changes in food related behavior connected to STN DBS weight gain (Macia, Perlemoine et al. 2004, Perlemoine, Macia et al. 2005, Montaurier, Morio et al. 2007, Bannier, Montaurier et al. 2009). Alternatively, body weight gain could be attributed to indirect factors such as decreased energy expenditure after DBS (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003, Montaurier, Morio et al. 2007). However, in a study comparing weight gain and energy intake after STN DBS versus pallidal DBS, changes in BMI were correlated with reduction of dyskinesias in the pallidal but not in the STN DBS group (Sauleau, Leray et al. 2009). This supports a direct or indirect effect of subthalamic stimulation on the hypothalamic homeostatic centers regulating energy balance, resulting in hormonal dysregulation and weight gain. Finally, for the sake of completeness, we must consider that decreased serum cortisol following DBS may simply be a non-specific observation, representing the reversal of a temporary perioperative increase in cortisol levels due to surgical stress (Desborough 2000).

In conclusion, our findings did not reveal the cause of weight gain in patients with PD treated by STN DBS. We found only physiological changes in peripheral food-related hormones corresponding to prevalent weight gain. Even if decreased cortisol production might be connected with STN DBS and lead to subsequent weight gain, direct effects of STN DBS on hypothalamic catabolic/anabolic peptide balance remain hypothetical and necessitate further elucidation.

5.4. Decrease in blood cortisol corresponds to weight gain following deep brain stimulation of the subthalamic nucleus in Parkinson's disease

It has been repeatedly shown that patients with Parkinson's disease gain body weight under treatment with deep brain stimulation of the subthalamic nucleus (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007). However, the mechanisms underlying this weight gain remain unclear. We, therefore, read with great interest the recently published article "The role of ghrelin, neuropeptide Y and leptin peptides in weight gain after deep brain stimulation for Parkinson's disease by Markaki et al (Markaki, Ellul et al. 2012). The authors performed body composition measurements and blood sampling before, and 3 and 6 months after STN DBS in 23 PD patients, looking for relations between WG and changes in blood levels of the metabolic hormones ghrelin, neuropeptide Y (NPY) and leptin. A significant weight gain (3.09±5kg, mean ±SD, p=0.007) was observed 3 months after surgery, with no further increase at 6 months. Also the circulating levels of NPY increased significantly (p=0.05) at 3 months, while the increase of ghrelin was significant only at 6 months (p=0.001). Weight gain was associated with changes of ghrelin and leptin levels at 3 and 6 months. The authors concluded that STN DBS may temporarily dysregulate the hypothalamic secretion of NPY and ghrelin, whereas the weight gain may be related to an increased production of ghrelin and leptin. These observations bear remarkable similarities to our earlier study, in which we assessed antropometric and hormonal profiles in 27 patients on the day of surgery and at 2,4,6 and 12 months on STN DBS (Novakova, Haluzik et al. 2011). Our patients' weight continuously increased throughout the study, with the mean body weight change with regard to baseline being +4.16 ±3.5kg ($p<0.001$) at 6 months and 5.18±5.8kg ($p<0.001$) at 12 months. Furthermore, in both studies, leptin and ghrelin levels correlates with body weight gain, corresponding to the known roles of the adpocyte-derived leptin and the orexigenic hormone ghrelin.

Curiously enough, Markaki at al (Markaki, Ellul et al. 2012) do not pay much attention to their own finding of markedly decreased cortisol levels following STN DBS. Nevertheless, this result is in surprisingly pecise agreement with our observation, probably shedding more light on the mechanisms of weight gain in Parkinson's disease following STN DBS (table 4).

		Baseline	1 month	2 months	3 months	4 months	6 months	12 months
Markaki et al. [4]	Cortisol, μg/dl	17.99	NA	NA	13.71	NA	15.81	NA
	Change to baseline, %		NA	NA	**−23.8**	NA	−12.1	NA
Novakova et al. [5]	Cortisol, nmol/l	688.96	618.78	524.26	NA	521.96	579.74	531.3
	Change to baseline, %		−10.2	**−23.9**	NA	**−24.2**	−15.9	**−22.9**

Table 4. Blood cortisol at different time points and its percent decrease versus baseline (Ruzicka, Novakova et al. 2012)

Bold print indicates significant changes. Conversion factor between conventional units (_g/dl) and SI units (nmol/l) for cortisol = 27.59 (source: http://www.globalrph.com/conv_si.htm). NA = Data not available.

At 3 months after STN DBS, Markaki et al (Markaki, Ellul et al. 2012) noticed a significant decrease in blood cortisol (-23.9%, p=0.027). In our study, cortisol levels decreased at 2 months, (-23.9%, p<0.002), still remaining significantly reduced compared to baseline at 12 months after DBS implantation (-22.9%, p=0.008) (Novakova, Haluzik et al. 2011). These results seem to indicate the involvement of hypothalamic-pituitary-adrenal axis in the mechanism of weight gain after STN DBS. It can by hypothesized that STN DBS acts on adjacent nerve fibers and structures including hypothalamic nuclei, where it suppresses secretion of corticotropin-releasing factor with a subsequent decrease in the production of cortisol. Since the level of corticotropin-releasing factor is low, its catabolic effect is mitigated; therefore, the homeostatic balance shifts towards predominance in anabolic reactions. Interestingly, it has been previously suggested that increased NPY levels are possibly related to diffusion of the electric current to the hypothalamus causing disruption of the melanocrotin system, leading to weight gain (Escamilla-Sevilla, Perez-Navarro et al. 2011).

Our hypothesis is indirectly supported by previous reports showing that cortisol levels were significantly higher in PD patients compared to healthy controls and that cortisol concentrations significantly decreased after levodopa intake, parkicularly in patients with a more advanced stage of PD (Charlett, Dobbs et al. 1998, Muller, Welnic et al. 2007). In fact, it has been demonstrated that PD patients lose weight throughout the progression of disease (Jaafar, Gray et al. 2010). The weight gain following STN DBS might thus mean a compensation of previous loss, rather than an excessive anabolic reaction. Accordingly, we suspect that the observation of a more sustained weight gain in our group may correspond to a lower initial body mass index than reported by Markaki et al. (25.8 vs 28.7), leading to a continued increase in weight in our patients, even if initial values were well above undernutrition in both groups (Novakova, Haluzik et al. 2011, Markaki, Ellul et al. 2012).

In conclusion, DBS in PD appears to act not only by exerting its motor effects trough the stimulation of the STN, but also by influencing non-motor functions, namely reversing catabolic processes and inducing weight gain, by diffusion of the electric current to the adjacent structures including hypothalamus and involving the hypothalamic-pituitary-adrenal axis.

6. Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease

6.1. Methods

Patients and weight measurement

Regular body weight measurements were made on the day of surgery and one, two, four, six, twelve and eighteen months after electrode implantation in 20 patients with advanced PD (6 women, 14 men; mean age 56.6±(SD)5.8 years; disease duration 13.2±4.5 years). A maximum change in weight during the study period and weight change at the 18th month were considered in each patient. Weight changes were expressed in absolute values as well as in percentage of initial body weight. Eating related questionnaires were administered at each visit. Food intake, hunger, general appetite and preference for sweet food were rated by patients as (0) without any change, (-1) lower or (+1) higher than at the previous visit.

Surgical procedure and stimulation settings

Bilateral DBS electrode implantation (model 3389, Medtronic, Minneapolis, MN, USA) was guided by MRI-based stereotaxy, microelectrode recordings and the test stimulation procedure as described elsewhere (Machado, Rezai et al. 2006). Within three days the electrodes were connected to a subcutaneously implanted pulse generator (Kinetra, Medtronic). Stimulation was initiated one month following implantation when each patient underwent standard screening of all electrode contacts in an off-medication state. Finally, one contact on each side and stimulation settings using a monopolar or bipolar (in one patient) setting were selected to obtain the best motor outcome. In the following month, the stimulation intensity was gradually increased (Figure 10) while dopaminergic medication was in most cases reduced to further optimize the motor outcome.

For the purpose of our study, stimulation intensity was calculated as the mean of arithmetic products of all the parameters from both neurostimulators (I-intensity, u-voltage, d-pulse duration, f-frequency): I= (uL.dL.fL+uR.dR.fR)/2 (Jech, Ruzicka et al. 2006). At month 18, the stimulation parameters were 2.860.5 V, 60–120 ms and 130 Hz and the mean stimulation intensity was 2.860.8. 104 V ms Hz.

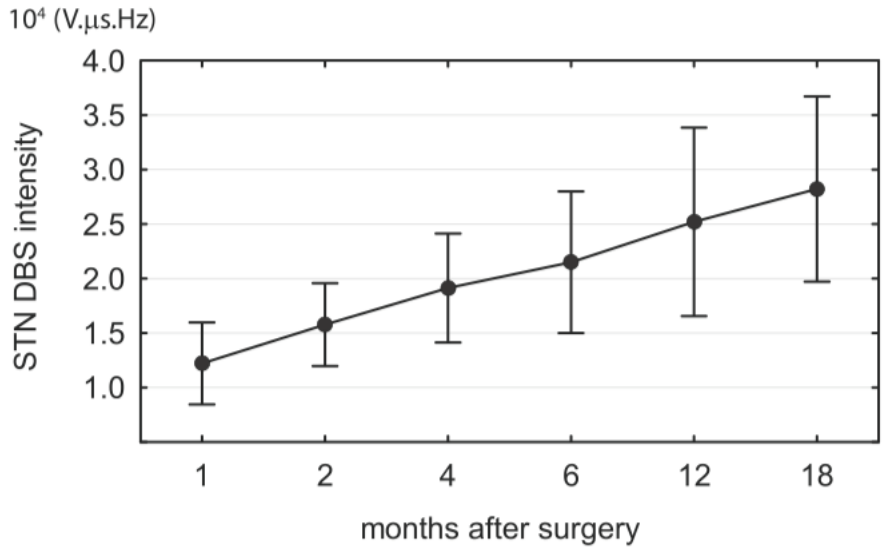


Figure 10. Mean stimulation intensity (±SD) of the STN DBS at 1, 2, 4, 6, 12 and 18 months after implantation in 20 patients with Parkinson's disease. The stimulation intensity was calculated as the arithmetic product of the I-intensity, u-voltage, d-pulse duration and f-frequency from both hemispheres (uL.dL.fL+uR.dR.fR)/2. The stimulation intensity was gradually increasing during the study to optimize the motor outcome.(Ruzicka, Jech et al. 2012)

Motor outcome assessment of STN DBS

Motor status was evaluated using the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Each subject was examined postoperatively under two conditions at least 12 hours after discontinuing all antiparkinsonian drugs: (1) in the off-neurostimulation state (sOFF) and (2) in the on-neurostimulation state (sON). The change of motor status induced by stimulation was expressed as the percentage of UPDRS-III (100- 100sON/sOFF). Additionally, hemi-body subscores derived from the UPDRS-III (items 20–26) were calculated as the sum of limb ratings of ridigity, akinesia and tremor, separately for the left and right extremities

Assessment of active contact position

Magnetic resonance images were acquired at 1.5 T on a Siemens Avanto system (Siemens, Erlangen, Germany) in each patient approximately one year after DBS implantation. To obtain better image resolution, sagittal (0.9 mm isotropic) and axial (1×1×1.6mm) T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were automatically coregistered and averaged using SPM5 software (Wellcome Trust Centre for Neuroimaging, London, UK). All four contacts (0,1,2,3) of the DBS electrode produced well defined susceptibility artifacts on the T1-MPRAGE image in each patient (Yelnik, Damier et al. 2003). While the coordinates of contacts 0 and 3 were established directly from the center of the distal and proximal artifacts using MRIcro 1.40 software (www.cabiatl.com/mricro), the coordinates of contacts 1 and 2 were calculated. The x coordinate of each contact was measured from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the midcommisural point. Two coordinate systems, native and normalized, were used in the study. During linear normalization, all dimensions were manually

adjusted with respect to the standardized AC-PC length, to the distance of the midcommissural point from the lateral edge of the putamen, and to the distance of the optic tract from the dorsal edge of the putamen. Finally, the active contacts in both hemispheres were plotted on axial (xy), coronal (xz) and sagittal (yz) planes covering the whole subthalamic area.

6.2. Analysis

Statistical analysis was performed using SPSS 14.0.1 software (SPSS Inc, Chicago, IL, USA). For parameters with normal distribution, parametric tests (one sample t-test, paried t-test, Pearson correlation analysis) were used. The others were assessed with the non-parametric tests (Friedman test, Spearman rank correlation analysis). Primary outcomes of the study were based on the maximum weight gain throughout the study and on the hemibody UPDRSIII in the sON state after initiation of neurostimulation. Their dependence on active contact position was analyzed for each x, y and z-axis separately by Pearson correlation analysis when considering the left and right hemispheres independently, as well as for all active contacts pooled bilaterally taking into account only one active contact (more medial or lateral contact from both hemispheres) in each patient. In addition, we systematically sought a border dividing the subthalamic area into regions with higher and lower risk of weight gain. To do so, we compared weight gain relative to the active contact position in the subthalamic area divided into two regions of interest (ROI) by a movable yz-plane in the mediolateral direction (x-axis). The iterative general linear model (GLM) was used to compare weight gain in patients with at least one contact within one ROI and patients with both contacts in the other ROI. The factor GENDER and covariates AGE and TIME of postoperative maximum weight gain were included to control for possible confounding effects. The division yz-plane was then successively moved along the x-axis by 0.5–1 mm steps to define a

BORDER with lowest p-value. A similar approach was used to compare weight gain considering active contacts in two subthalamic ROIs separated by a movable xz-plane in the anteroposterior direction (y-axis) and by the xy-plane in the ventrodorsal direction (z-axis). Relationships between body weight, motor performance, eating behavior and intensity of stimulation were assessed separately as secondary outcomes. As they were based on multiple comparisons, the Bonferroni correction was applied whenever appropriate.

6.3. Results

After initiation of STN DBS, the UPDRS-III score dropped on average from 36.76(SD)9.6 (sOFF) to 17.865.5 (sON) ($T = 7.3$, $p < 10^{-7}$) showing good efficacy of neurostimulation treatment. The maximum change in body weight in the eighteen-month period after implantation was on average +6.9 kg64.5 kg (20.3 to +18.3 kg) and was strongly significant ($T = 6.6$, $p < 10^{-5}$). Despite gradually increasing weight during the entire study period (Figure 11), nine patients reached the maximum body weight within the first 6 months after surgery, five patients in months 6– 12 and six patients in months 12–18 after surgery. As the analyses of active contact coordinates derived from native and normalized approaches yielded similar results, only statistics based on coordinates in native space are reported. In individual patients, the maximum weight gain correlated inversely along the x-axis with the distance of the active contact from the wall of the third ventricle in the left hemisphere ($r = -0.48$, $p < 0.05$), right hemisphere ($r = -0.50$, $p < 0.05$), and in pooled data ($r = -0.55$, $p < 0.01$) if only more medial active contact regardless to hemisphere was considered (Figure 12). Similar results were obtained for maximum weight gain expressed in percentage of initial body weight as well as when considering weight gain at the end of the 18th month. In addition, the hemi-body UPDRS-III subscores in sON condition inversely correlated with the distance of the contralateral active contact from

the wall of the third ventricle in the mediolateral direction (r =-0.42, p<0.01) (Figure 13). However, none of these parameters showed any relation to the active contact position along the y-axis or z-axis.

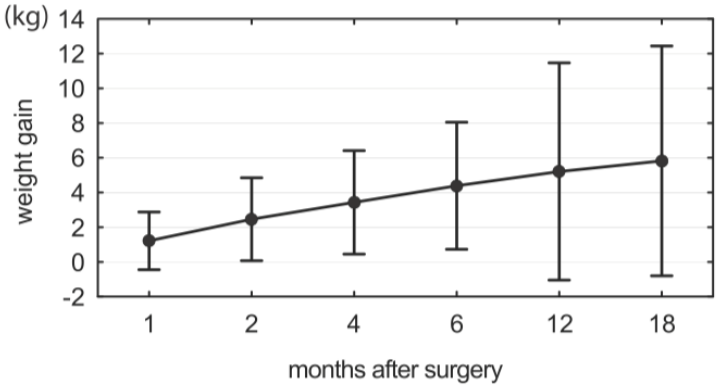


Figure 11. Mean changes in weight after implantation in 20 patients with Parkinson's disease. Body weight gradually increased during the study period. Weight gain represents the difference in weight (±SD) compared to the preoperative state (Ruzicka, Jech et al. 2012)

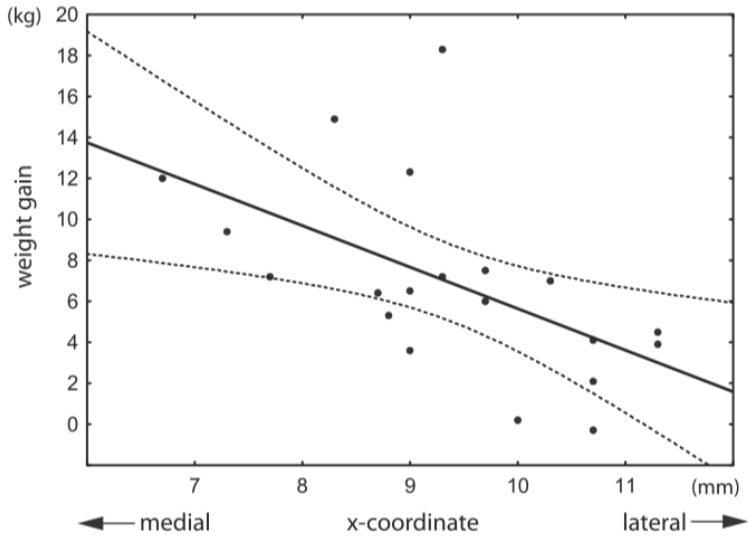


Figure 12. Weight gain in 20 patients with Parkinson's disease in relation to the mediolateral position of the active contact with bilateral STN DBS (r = 20.55, p<0.01). Only one active contact (more medial contact from both hemispheres) was used in each patient. The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Each millimeter in the medial direction was associated on average with a 1.6-kg increase in body weight. Dotted lines denote the 95% confidence interval of the regression line. (Ruzicka, Jech et al. 2012)

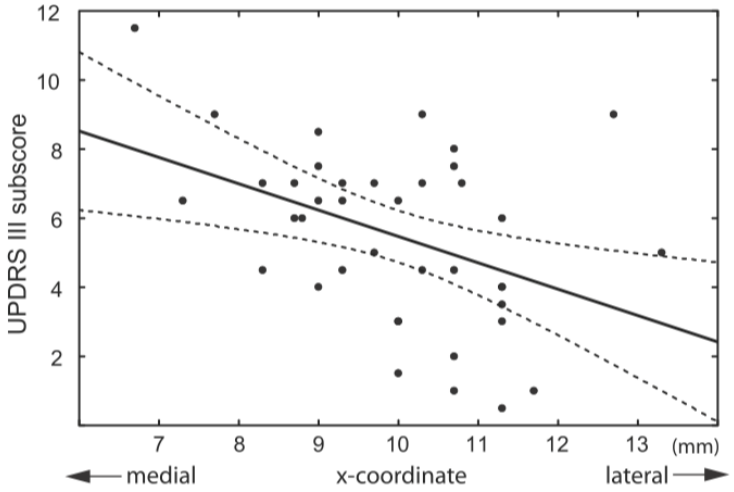


Figure 13. Hemi-body UPDRS-III subscores in the sON condition after overnight withdrawal of dopaminergic therapy in relation to the mediolateral position of the contralateral active contact. After initiation of STN DBS, the hemi-body side with the lowest motor score (best motor condition) had the contralateral contacts located more laterally from the wall of the third ventricle ($r = -0.42$, $p<0.01$). Dotted lines denote the 95% confidence interval of the regression line (Ruzicka, Jech et al. 2012).

With the iterative moving plane approach, we found a border orthogonal to the x-axis dividing the subthalamic area into two ROIs that differed in postoperative weight gain. Patients with at least one active contact within 9.3 mm of the wall of the third ventricle demonstrated significantly greater weight gain (9.4±4.4 kg, N= 11) than those patients with both contacts located more laterally from the wall (3.9±2.7 kg, N=9) (GLM, factor BORDER: $F = 16.1$, $p<0.001$)(Figure 14). The postoperative maximum weight gain significantly differed between genders, with a greater increase in women (N = 6, 10.9±(SD)4.8 kg) than in men (N = 14, 5.2±3.4 kg) (GLM, factor: GENDER, $F = 10.7$, $p<0.01$). However, no other covariates (factor AGE: $F= 0.001$, $p = 0.99$; factor TIME: $F = 0.002$, $p = 0.96$) nor interactions between BORDER, GENDER, AGE and TIME were significant.

In addition, the postoperative maximum weight gain in all patients inversely correlated with preoperative body weight ($r =-0.62$, $p<0.05$ corrected). Maximum weight gain did not significantly depend on UPDRS-III improvement

after switching the stimulation on (r =-38, p =0.1), and no correlation between weight gain at the 18th month and stimulation intensity was found. Analysis of eating behavior failed to demonstrate any change in hunger, appetite, preference for sweet food or food intake in our patients. However, there was a positive correlation between food intake and body-weight gain at the 18th month (rho = 0.66, P<0.05 corrected).

6.3. Discussion

We observed weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 12), and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally (Figure 14). Thus, our results are consistent with the hypothesis that STN DBS exerts a regional effect on adjacent structures involved in energy balance. In addition, our findings are also in agreement with reports of weight gain observed after unilateral STN DBS (Walker, Lyerly et al. 2009, Lee, Kurundkar et al. 2011). As the position of each implanted electrode was verified by intraoperative microrecording and DBS caused clear motor improvement, we believe that our observations are not affected by electrode misplacement outside the STN. However, no correlation between stimulation intensity (Figure 10) and weight gain (Figure 11) was found in our study. This may be partly explained by low variability of stimulation parameters between patients or limited size of the patient group. The maximum weight gain in our study was significantly larger in women than in men. Although women may be more susceptible to weight gain (Mueller, Anwander et al. 2011), previous studies have proven no significant sex-related differences in weight gain after unilateral or bilateral STN DBS (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007, Bannier, Montaurier et al. 2009, Walker, Lyerly et al. 2009, Lee, Kurundkar et al.

2011).These findings are in agreement with our observation that weight gain in all six women of our study was associated with the medial contact site and that no interaction between active contact position and gender was found. Similar to other studies (Hamani, Saint-Cyr et al. 2004, Herzog, Fietzek et al. 2004, Godinho, Thobois et al. 2006), we found an inverse correlation between unilateral motor outcome (measured for rigidity, akinesia and tremor using hemi-body UPDRS-III subscore) and contralateral position of the active contact (Figure 13). Thus, patients with the lowest motor score (best motor condition) had contacts located more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part located dorsolaterally in the nucleus (Hamani, Saint-Cyr et al. 2004). However, we did not observe any significant correlation between weight gain and change in UPDRS-III score. This finding is consistent with those published previously (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Sauleau, Leray et al. 2009) and may indicate that the connection between changes in weight and motor outcomes is not as straightforward as has been proposed (Gironell, Pascual-Sedano et al. 2002). Unrelated weight gain to motor outcome was also shown in another study in which weight gain was more pronounced in patients with subthalamic stimulation than in patients with pallidal stimulation, despite similar motor improvement in both groups (Sauleau, Leray et al. 2009). Thus, additional factors likely contribute to greater weight gain in subthalamic stimulation.

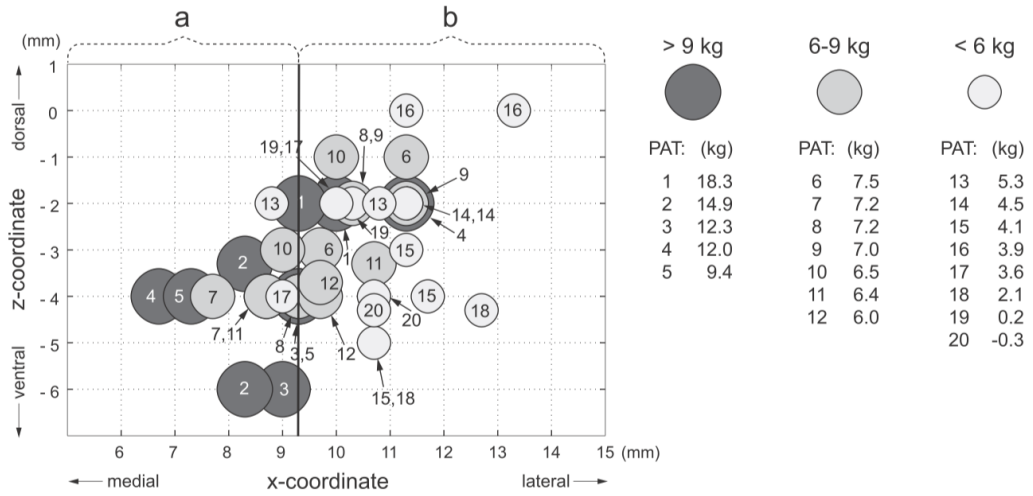


Figure 14. Bilateral STN DBS active contact positions of 20 patients with Parkinson's disease plotted in the coronal plane with respect to weight gain. Patients (N = 11) with at least one active contact (a) placed within 9.3-mm of the wall of the third ventricle gained significantly more weight than patients (N = 9) with both contacts (b) located more laterally (p,0.001) (Ruzicka, Jech et al. 2012)

The central mechanism by which STN DBS might cause weight gain remains unclear. It could be hypothesized that the spread of stimulation current beyond the borders of the STN may influence the hypothalamic regulation of energy metabolism or the homeostatic pathway of food intake. However, there are so far only a few studies on the effects of long-term STN DBS on autonomic (Priori, Cinnante et al. 2001, Holmberg, Corneliusson et al. 2005, Ludwig, Remien et al. 2007) or hormonal systems (Novakova, Haluzik et al. 2011), and they have provided no clear explanation for weight gain. Conversely, increased food intake by non-homeostatic or reward mechanisms may also provide a compelling hypothesis. The medial tip of the STN is involved in basal ganglia limbic and motivational functions (Temel, Blokland et al. 2005, Haegelen, Rouaud et al. 2009, Lardeux, Pernaud et al. 2009, Rouaud, Lardeux et al. 2010). It is connected to key structures of the reward system such as the ventral pallidum and the ventral tegmental area (Groenewegen and Berendse 1990, Groenewegen, Berendse et al. 1993, Parent and Hazrati 1995). It has been shown that STN DBS can affect the neural activity of these structures, as well as increase

dopaminergic transmission in the striatum (Turner, Lavin et al. 2001, Winter, Mundt et al. 2008, Shon, Lee et al. 2010). Moreover, the medial part of the STN is adjacent to the medial forebrain bundle which contains essential projections underlying reward functions (Wise 2005). Extensive research has demonstrated a close relationship between the mesolimbic system, medial forebrain bundle and ventral pallidum in motivational desire for food rewards, increase in food intake and obesity (Beaver, Lawrence et al. 2006, Davis, Patte et al. 2007, Berridge 2009, Smith, Tindell et al. 2009). Therefore, it seems plausible that an active electrode in the proximity of the medial STN could be ideally positioned to stimulate the reward system, thereby contributing to changes in motivational behaviors related to food intake and weight gain. Our previous study supports this hypothesis, as it revealed that postoperative weight gain correlated with arousal ratings from food pictures in the STN DBS ON condition, suggesting an altered attribution of incentive salience (i.e., emotional relevance) to rewarding stimuli (Serranova, Jech et al. 2011). Although most of the subjects did not report any changes in food intake, hunger or appetite in our study, the inaccuracy of self reported intake (Schoeller 1990, Hill and Davies 2001, Jakes, Day et al. 2004) should prompt caution in the interpretation of these results. Food intake depends largely on reward or homeostatic systems and is only partly under cognitive control (Peters, Wyatt et al. 2002, Davis, Patte et al. 2007, Berridge, Ho et al. 2010). We can hypothesize that slight individual changes in motivational behavior and reward system induced by DBS of subcortical structures need not be reflected in subjective feelings such as hunger or appetite (Winkielman, Berridge et al. 2005, Serranova, Jech et al. 2011). Further prospective studies taking into account changes in sensitivity to reward (Davis, Patte et al. 2007) and actual food intake would be necessary to clarify this question. In agreement with another study (Bannier, Montaurier et al. 2009),

we found a significant inverse correlation between preoperative body weight and postoperative weight gain. Since weight has been reported to decrease with PD progression (Bachmann and Trenkwalder 2006), it has been suggested that patients treated with DBS normalize their weight compared to their premorbid status because of motor improvement (Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007). However, this hypothesis cannot fully account for the fact that although most patients indicated for DBS are normal weight or overweight, the majority of them experience continuous weight gain after surgery (Barichella, Marczewska et al. 2003, Bannier, Montaurier et al. 2009). Yet it seems that changes in motor manifestations and energy expenditure can only partly explain both the weight loss in PD and weight gain after initiation of DBS (Bachmann and Trenkwalder 2006, Delikanaki-Skaribas, Trail et al. 2009, Sauleau, Leray et al. 2009). It has been shown that overweight and obese individuals have higher sensitivity to reward which predicts the tendency for overeating and strengthens preferences for sweet and fatty foods (Davis, Patte et al. 2007). We speculate that if STN DBS increases sensitivity to reward in relation to the medial contact site in the subthalamic area, thereby modulating eating behavior, this effect would be more pronounced especially in patients with preoperatively lower body weight, lower sensitivity to reward and without previous, excessive caloric intake. Some limitations have to be taken into account when interpreting our results. Since body weight may be reflected in local white matter changes (Mueller, Anwander et al. 2011) and the size and position of the STN varies (Richter, Hoque et al. 2004, Daniluk, K et al. 2010) to some extent relative to the midcommisural point, the influence of anatomic variability cannot be excluded from our measurements. However, we compensated for the variable width of the third ventricle, which significantly affects the mediolateral position of the STN (Zhu, Hamel et al. 2002, Daniluk, K

et al. 2010), by measuring the x coordinate from the wall of the third ventricle. In conclusion, our findings support the hypothesis that weight gain in PD patients treated by STN DBS may, at least in part, result from the regional effect of stimulation on adjacent structures involved in the central regulation of energy balance or reward.

7. Conclusions and summary of the field

1. We observed weight gain following STN DBS in all studied patients in retrospective study, the weight gain was accompanied by motor improvement. Women tended to gain more weight than men which was in contrary to other reports. Weight gain was accompanied by an increase in body mass index with number of patients shifting BMI category. We found that if observing patients for longer interval after STN DBS the weight fluctuations are still existing. Thus our findings are consistent with hypothesis that advanced PD patients treated with STN DBS gain weight.

2. Weight gain in our group of patients did not correlate with any clinical variables of motor improvement nor with the reduction of dopaminergic treatment following STN DBS which is in agreement with literature.

3. We observed increase in body weight, BMI, weight circumference and body fat percentage during the entire prospective study. Significant body weight gain was already noticed at one moth following STN DBS. We found that body weight and BMI differed significantly in genders, with greater increase in women.

4. Besides cortisol we found no significant changes in tested hormones and food related parameters. There was a positive correlation between leptin levels and body weight and body fat percentage. Body weigh also negatively correlated with adiponectin, positively with ghrelin. These finding reflect physiological regulatory mechanisms of food homeostasis. Thus, the findings indicate that changes in peripheral food related hormones do not appear to be causing weight gain in this patient population. We may speculate that there is direct or indirect effect of subthalamic stimulation on the hypothalamic homeostatic centers regulating energy balance, resulting weight gain.

5. Significant decrease of cortisol levels compared to baseline was observed in our study. Thus direct effect of STN stimulation on adjacent fibers and nuclei was considered. We may speculate that STN DBS acts on the hypothalamus by suppressing the secretion of CRF with subsequent decrease in the production of cortisol, leading to a predominance in anabolic reactions.

6. We found that weight gain inversely correlates to the distance of the contacts from the wall of the third ventricle. Patients with at least one contact positioned medially within the STN encountered significantly higher weight gain that those patients with both active contacts localized laterally. We may therefore speculate that STN DBS exerts regional effects on neighboring structures involved energy homeostasis.

Summary of the field

Deep brain stimulation of the subthalamic nucleus (STN DBS) is recognized as a standard and effective treatment method for motor symptoms of advanced Parkinson's disease.

About 15 years ago first reports of weight gain after STN DBS in PD patients have emerged. Since than these findings were reciprocated by numerous works and weight gain is now recognized as a common side effect seen in PD patients undergoing STN DBS (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Tuite, Maxwell et al. 2005, Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Bannier, Montaurier et al. 2009, Sauleau, Leray et al. 2009, Strowd, Cartwright et al. 2010, Novakova, Haluzik et al. 2011, Ruzicka, Jech et al. 2012, Strowd, Herco et al. 2016). We now acknowledge that it is not only a "simple" weigh gain, but that number of patients are becoming overweight or even obese which subsequently predisposes them to multiple pathological conditions associated mainly with metabolic syndrome. Also it has been considered that significant weight gain increases functional disability which is already reduced in this patient population. Therefore all PD patients planned for STN DBS are now uniformly informed of this frequent side effect; careful monitoring of weight is recommended and potential referral to dietician counselling might be also needed in case of excessive weight gain.

In agreement, patients evaluated in our studies also gained weight following STN DBS and it was accompanied by increase in BMI and other antropometric parameters (Novakova, Ruzicka et al. 2007, Novakova, Haluzik et al. 2011, Ruzicka, Jech et al. 2012). The mean increase of weight was in line with increases reported by others.

The mechanisms behind the weight gain have been of interest of many movement disorders teams and extensive efforts have been put in place to elucidate these outcomes. Some of the most logical justifications which comes to everyone's mind such as that the weight gain is related to normalization of energy expenditure due to decreased rigidity and improvement in dyskinesias or to the reduction in dopaminergic therapies were however not confirmed across all studies (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Balestrino, Baroncini et al. 2017). Number of studies also failed to report any modification of food intake or appetite in these patients (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007, Novakova, Haluzik et al. 2011).

Our research group hypothesized that weight gain is associated with hormonal dysregulation of energy homeostasis and food intake, however we failed to demonstrate non-physiological variation of food related hormones. There have been Interestingly, consistently with Greek colleagues (Markaki, Ellul et al. 2012), we found markedly reduced morning cortisol levels following STN DBS (Novakova, Haluzik et al. 2011, Ruzicka, Novakova et al. 2012) which we thought can influence food regulation by shifting homestatic balance to anabolic state. Other teams interested at the STN DBS effect on the hypothalamic –pituitary-adrenal axis (HPA) however failed to reciprocate the cortisol changes findings (Seifried, Boehncke et al. 2013), however the methodology may be responsible for this contradictory findings (Ruzicka, Jech et al. 2015).

Our observations are further supported by structural and functional complexity of subthalamic area, its proximity to the structures involving regulation of energy expenditure and food intake and potential exertion of regional effects of STN DBS on these regions accounting for weight gain after the procedure.

Our group have further looked at position of active electrode contact which has been postulated as an important predictor of weight gain, finding that patients with at least one contact located medially in the STN experience greater weight gain than those with both active contacts located laterally (Ruzicka, Jech et al. 2012), this finding was recently confirmed by additional report (Balestrino, Baroncini et al. 2017). Team led by Dr. Ruzicka has also confirmed our previous postulation that DBS-STN exerts influence on the HPA axis by confirming that morning cortisol changes are in close relation to the mediolateral position of the active electrode within the STN. The team has further found that the cortisol changes are accompanied by increased postoperative anxiety and that patients with higher anxiety and lower cortisol levels have higher weight gain than those with lower anxiety (Ruzicka, Jech et al. 2015)

The role of STN in emotional and motivational processing is also well recognized and thus speculating that motivational and associative aspects of food behavior account or at least be associated with weight gain after STN DBS surgery is certainly of interest. PET study was used to analyze correlation between changes in brain metabolism and weight gain after STN DBS confirming correlations in brain metabolism in limbic and associative areas, including the orbitofrontal cortex, lateral and medial parts of the temporal lobe, anterior cingulate cortex and retrosplenial cortex. (Sauleau, Le Jeune et al. 2014) confirming that changes in associative and limbic processes contribute to weight gain after STN DBS.

Indeed, it has been confirmed increased motivational relevance of aversive stimuli together with increased sensitivity to food reward cues in PD patients with post-operative weight gain. It has been reported that wanting low calorie food, not liking is associated with weight gain (Aiello, Eleopra et al. 2017).

In conclusion, weight gain is a frequent non-motor side effect of STN DBS. Putative mechanisms behind this weight gain have been extensively discussed in literature.

Based on the current knowledge it is believed that the weight gain is of multifactorial origin.

8. Abbreviations list

AP area postrema
AgRp Agouti related protein
ARC nucleus arcuatus
ACTH Adreno corticotrophine hormone
AN anorexia nervosa
AMPK 5' AMP-activated protein kinase
BBB blood brain barrier
BMI body mass index
BW body weight
CART Amphetamine regulated transcript
CNS central nervous system
CSF cerebrospinal food
CRF Corticotropin releasing factor
CRH Corticotropin releasing hormone
CCK Cholecystokinin
DBS deep brain stimulation
DEE daily energy expenditure
DVC dorsal vagal complex
EE energy expenditure
ENS enteral nervous system
GABA Gamma-Aminobutyric Acid
GIT gastrointestinal tract
GIP gastric inhibitory peptide
GLP-1 Glucagon like peptide -1
HMW high molecular weight
LHA lateral hypothalamic area
mRNA messenger Ribonucleic acid
MCI mild cognitive impairment
MDS Movement disorders society
MSH melanocyte stimulating hormone
NMS non-motor symptoms
NPY Neuropeptid ypsilon
ON
OFF
PD Parkinson’s disease
POMC Propiomelanocortin
PVN nucleus paraventricularis
REE resting energy expenditure
SN substantia nigra
STN subthalamic nucleus
T2DM type 2 diabetes mellitus
UPDRS Unified Parkinson’s Disease Rating Scale
VTA ventral tegmental area
WC waist circumference

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10. Publications

Original articles related to the Thesis:

Novakova, L., M. Haluzik, R. Jech, D. Urgosik, F. Ruzicka, and E. Ruzicka. 2011. 'Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation', Neuro Endocrinol Lett, 32: 437-41. **IF - 1.296**

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Ruzicka, F., R. Jech, L. Novakova, D. Urgosik, J. Vymazal, and E. Ruzicka. 2012. 'Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease', PLoS One, 7: e38020. **IF- 3.73**

11. Publications in extenso

Ruzicka, F., R. Jech, L. Novakova, D. Urgosik, O. Bezdicek, J. Vymazal, and E. Ruzicka. 2015. 'Chronic stress-like syndrome as a consequence of medial site subthalamic stimulation in Parkinson's disease', *Psychoneuroendocrinology*, 52: 302-10. **IF- 4.704**

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Published chapters in medical books

Nováková L.: Diabetické neuropatie. Praktická diabetologie. Aeskulap. 2009

Nováková L.: Diabetické neuropatie. Praktická diabetologie. Aeskulap. 2013

12. Suplement

Novakova, L., E. Ruzicka, R. Jech, T. Serranova, P. Dusek, and D. Urgosik. 2007. 'Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease', Neuro Endocrinol Lett, 28: 21-25.

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